Entwicklung und Evaluation von

cataCXium® F

Phosphinliganden für palladiumvermittelte Kreuzkupplungen

TECHNISCHE UNIVERSITÄT DARMSTADT

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D17

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Teile dieser Arbeit sind bereits veröffentlicht oder zur Veröffentlichung eingereicht:

[1] Christoph A. Fleckenstein, Herbert Plenio, *"Redox-Switchable Phase Tags-Facile Mitsunobu Reactions using Ferrocenyl-Tagged Triphenylphosphine"*, *Adv. Synth. Catal.* **2006**, *348*, 1058-1062.

[2] Christoph A. Fleckenstein, Herbert Plenio, *"9-Fluorenyldialkylphosphines for the Pd-Catalyzed Sonogashira, Suzuki and Buchwald-Hartwig Coupling in Organic Solvents and in Water"*, *Chem. Eur. J.* **2007**, *13*, 9, 2701-2716.

[3] Christoph A. Fleckenstein, Herbert Plenio, *"1-Indenyldialkylphosphines and Cyclopentadienyldialkylphosphines as Ligands for High-Activity Palladium-Catalyzed Cross-Coupling Reactions with Aryl Chlorides"*, *Organometallics*, **2007**, *26*, 10, 2758-2767.

[4] Christoph A. Fleckenstein, Sutapa Roy, Steffen Leuthäußer, Herbert Plenio, *"Sulfonated N-Heterocyclic Carbenes for Suzuki Coupling in Water", Chem. Comm.* **2007**, *27*, 2870-2872.

[5] Christoph A. Fleckenstein, Herbert Plenio, *"Aqueous Cross Coupling: Highly Efficient Suzuki-Miyaura of N-Heteroaryl Halides and N-Heteroarylboronic Acids"*, *Green Chem.* **2007**, *9*, 12, 1287-1291.

[6] Christoph A. Fleckenstein, Renat Kadyrov, Herbert Plenio, *"Efficient large Scale Synthesis of 9-Alkylfluorenyl Phosphines for Pd-Catalyzed Cross Coupling Reactions"*, *Org. Process Res. Dev.* **2008**, *12*, 475-479.

[7] Christoph A. Fleckenstein, Herbert Plenio, *"Aqueous/Organic Cross Coupling: Sustainable Protocol for Sonogashira Reactions of Heterocycles"*, *Green Chem*. **2008**, *10*, 563-570.

[8] Christoph A. Fleckenstein, Herbert Plenio, *"Highly Efficient Suzuki-Miyaura Coupling of Heterocyclic Substrates through Rational Reaction Design"*, *Chem. Eur. J.* **2008**, *14*, 4267-4279.

[9] Christoph A. Fleckenstein, Herbert Plenio, *"Efficient Suzuki-Miyaura Coupling of (Hetero)aryl Chlorides with Thiophene- and Furanboronic Acids in Aqueous n-Butanol"*, *J. Org. Chem.* **2008**, *73*, 8, 3236-3244.

[10] Christoph A. Fleckenstein, Herbert Plenio, *"Pd-Complexes of Bidentate Fluorenylphosphines and the Influence of the Bridging Unit on Pd-Catalyzed Cross Coupling Reactions"*, *Organometallics*, **2008**, zur Publikation angenommen.

[11] Herbert Plenio, Christoph Fleckenstein, Renat Kadyrov, Juan Almena, Axel Monsees, Thomas Riermeier (Evonik Degussa GmbH), *„New Cyclopentadienyl, Indenyl or Fluorenyl Substituted Phosphine Compounds and their Use in Catalytic Reactions"*, WO2008025673, **2008**.

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Ob eine Sache gelingt, erfährst Du nicht,
wenn Du darüber nachdenkst,
sondern wenn Du sie ausprobierst.

(Werner Bethmann)

Inhaltsverzeichnis

Abkürzungsverzeichnis

Abb.	Abbildung
Ad	Adamantyl
API	active pharmaceutical ingredient
Ar	Aryl
Binol	1,1‘-Bi-2-naphthol
biph	Biphenyl
Bn	Benzyl
Boc	*tert*-Butyloxocarbonyl
*n*Bu	*n*-Butyl
*t*Bu	*tert*-Butyl
Cp*	Pentamethyl-cyclopentadienyl
Cy	Cyclohexyl
DABCO	1,4-Diazabicyclo[2.2.2]-octan
dba	Dibenzylidenaceton
DEAD	Diethylazodicarboxylat
DFT	Dichtefunktionaltheorie
DMF	Dimethylformamid
Et	Ethyl
Fc	Ferrocenyl
Flu	Fluorenyl
Fmoc	Fluorenylmethoxycarbonyl
ggf.	gegebenenfalls
L	Ligand
LDA	Lithiumdiisopropylamid
Me	Methyl
MESP	molecular electrostatic potential
*N*HC	*N*-Heterocyclisches Carben
NMR	nuclear magnetic resonance
OAc	Acetat
OMes	Mesylat
ONf	Nonaflat
OTf	Triflat
OTos	Tosylat
Ph	Phenyl
ppm	parts per million
Pr	Propyl
QALE	quanitative analysis of ligand effects
RT	Raumtemperatur
S_E	elektrophile Substitution
S_N	nucleophile Substitution
TEP	Tolman electronic parameter
THF	Tetrahydrofuran
TMEDA	*N*,*N*,*N*‘,*N*‘-Tetramethyl-ethylendiamin
TOF	turn over frequency
TON	turn over number
TPP	Triphenylphosphin
TPPTS	Triphenylphosphintri-sulfonat
TsOH	Toluolsulfonsäure
vs.	versus

1. Einleitung

1.1. Palladiumkatalysierte Kreuzkupplungsreaktionen

Palladiumkatalysierte Kreuzkupplungsreaktionen entwickelten sich in den letzten dreißig Jahren zu außerordentlich leistungsfähigen und vielseitigen Werkzeugen der organischen Synthesechemie.[1-8] Einige wichtige Pd-katalysierte Kreuzkupplungsreaktionen sind in Abbildung 1 dargestellt. Die Heck-Mizoroki-Kupplung,[9-13] die Heck-Carbonylierung / Alkoxycarbonylierung[14-16] sowie die Cyanierung[17-20] gehören zu den ersten, in den frühen 1970er Jahren entdeckten Reaktionen dieser Art.

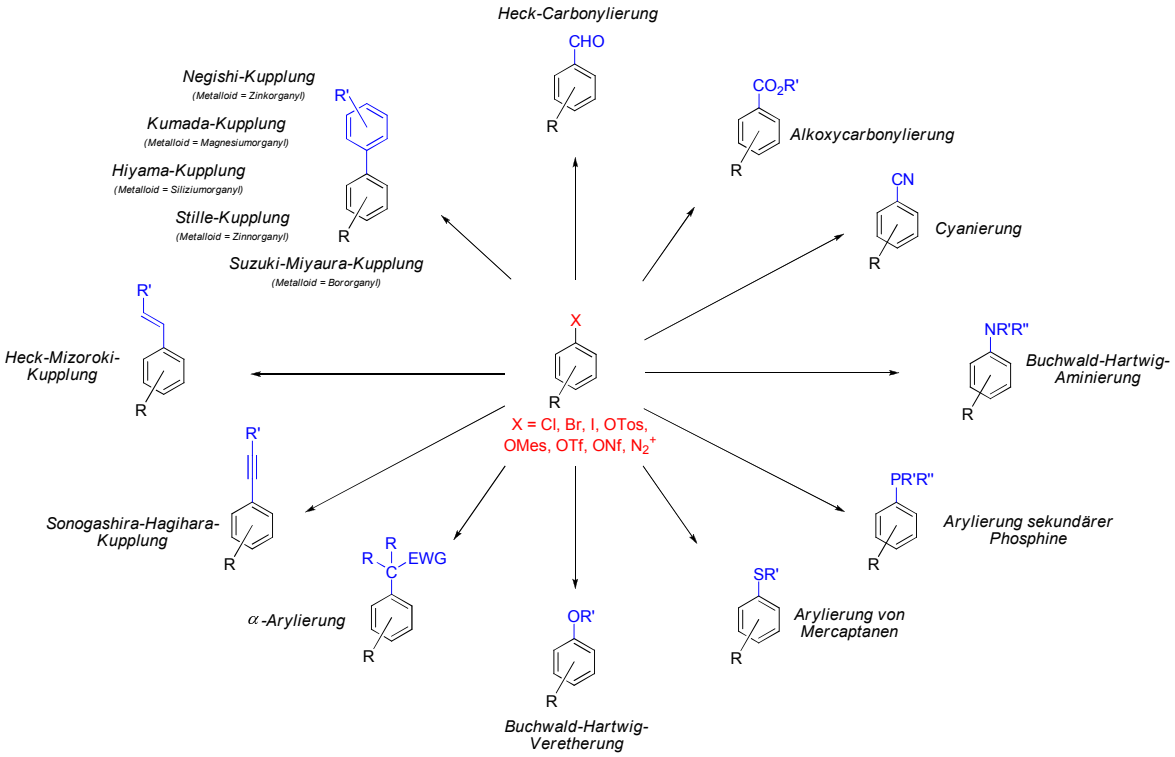


Abbildung 1. Ausgewählte palladiumkatalysierte Kreuzkupplungsreaktionen.

Weitere C-C-verknüpfende Kreuzkupplungsreaktionen wie die Suzuki-Miyaura-,[21-25] Negishi-,[26][8, 27, 28] Kumada-,[8, 29-31] Hiyama-, [32-34] Stille-[35-38] und die Sonogashira-Hagihara-Kupplung[39-41] sowie eine breite Vielfalt von *α*-Arylierungen an CH-aciden Substraten[42-45] stellen ebenfalls wichtige Varianten dieses Reaktionstyps dar. Von keinem geringeren Interesse sind C_{sp^2}-Heteroatom-verknüpfende Kreuzkupplungsreaktionen, zu denen die ca. zwanzig Jahre später erstmals erwähnte C-N-verknüpfende Buchwald-Hartwig-Aminierung,[46-51] die wenig später entwickelte C-O-verknüpfende Buchwald-

Hartwig-Veretherung[52-54] sowie C-S-[55-57] bzw. C-P-verknüpfende[58, 59] Reaktionen zu rechnen sind.

Als katalytisch aktive Spezies für Pd-Kreuzkupplungen wird in Lösung befindliches Pd^0 angenommen, welches auf unterschiedliche Weisen eingetragen oder generiert werden kann.[60] Die einfachsten und zuerst eingesetzten Palladiumquellen sind Pd^{II}-Salze wie $Pd(OAc)_2$ oder $PdCl_2$, welche unter den entsprechenden Reaktionsbedingungen zu Pd^0 reduziert werden. Freies Pd^0 tendiert in Lösung zur Agglomeration und zur Ausbildung von sogenanntem „Palladiumschwarz“, das eine deutlich geringere katalytische Aktivität aufweist. Durch Zugabe von Additiven wie etwa Tetraalkylammoniumbromid,[61] welches katalytisch aktive, nanometerdimensionierte Pd-Kolloide stabilisiert, lässt sich diese Agglomeration deutlich bremsen. Alternativ findet vielfach auch Palladium Anwendung, das auf anorganischen Materialien, Kohlenstoff oder Polymeren heterogen geträgert ist. Man geht davon aus, dass auch bei diesen heterogenen Katalysatoren in die Reaktionslösung diffundierendes Pd^0 die katalytisch aktive Spezies ist und daher die eigentliche Katalyse ebenfalls homogen abläuft.[60, 62, 63] *Köhler* konnte zeigen, dass sich das Pd nach der Kupplungsreaktion wieder auf dem festen Trägermaterial ablagert.[60, 64] Eine gute Übersicht über heterogen katalysierte Pd-Kreuzkupplungen bietet ein kürzlich von *Yin* und *Liebscher* verfasster Übersichtsartikel.[65]

Bei rein homogen katalysierten Kreuzkupplungsreaktionen vermögen elektronendonierende Liganden, die Pd^0-Spezies in Lösung zu stabilisieren und so Agglomeration und Katalysatorinhibierung zu vermeiden. Als leicht zugängliche und stabile Liganden fanden Triarylphosphine[66] recht früh Verwendung zur Stabilisierung des Pd und werden aus ökonomischen Gründen auch heute noch vielfach eingesetzt, z.B. in Form von $(PPh_3)_2PdCl_2$ oder $Pd(PPh_3)_4$.[7, 39, 40, 67] Pd-Komplexe des elektronenärmeren Tri-2-furylphosphins konnten sich nur in Pd-vermittelten Stille-Kupplungen[68] gegen PPh_3 durchsetzen,[69, 70] zeigten sich jedoch in anderen Kupplungsreaktionen, beispielsweise der Heck-Kupplung von Arylbromiden, unterlegen.[71] Wie man feststellen konnte, erfordert die Umsetzung schwierigerer Kupplungssubstrate wie z.B. Arylchloride den Einsatz elektronenreicherer und sterisch anspruchsvollerer Liganden.[72, 73] Elektronendonierende Liganden steigern die Nucleophilie des Pd^0-Komplexes und erleichtern so die oxidative Addition in die Halogen-Kohlenstoff-Bindung. Sterisch anspruchsvolle Liganden beschleunigen den katalytischen Schritt der reduktiven Eliminierung, die zur Freisetzung des Produkts und Regeneration des Pd^0-Katalysators führt. Entsprechende Modifikation der Triphenylphosphinliganden führten zum Einsatz von etwas elektronenreicheren und sterisch anspruchsvolle-

ren Tri-*o*-tolyl- oder Tri-2,6-xylylphosphinen.[74] Die katalytische Aktivität der entsprechenden Pd-Komplexe ist jedoch in der Regel bescheiden.

Mittlerweile ist eine kaum noch überschaubare Vielfalt an leistungsfähigen Liganden oder Pd-Katalysatoren bekannt, welche den Umsatz eines breiten Spektrums aktivierter und deaktivierter Substrate inklusive Arylchloride ermöglichen. Neben den einzähnigen Phosphinliganden des Typs PR_3 sind Palladacyclen,[14, 75-82] *N*-Heterocyclische Carbene,[83][79, 81, 84-91] Phosphite,[92-94] Phosphoramidite,[93] *P*,*N*-,[5, 62, 95, 96] *P*,*O*-[5, 62, 96] oder *N*,*N*-[5, 95] Bidentatliganden die am häufigsten vertretenen Ligandenklassen. Insbesondere die *N*-Heterocyclischen Carbene, die auch in der Olefinmetathese[97-99] und Organokatalyse[100, 101] breite Anwendung finden, etablierten sich in den vergangenen Jahren als eine Ligandenklasse mit großem Potential für Pd-vermittelte Kreuzkupplungsreaktionen.

Eine umfassende Betrachtung der vielfältigen hier genannten Ligandenklassen in Bezug auf palladiumkatalysierte Kreuzkupplungen ist im Rahmen dieser Arbeit nicht möglich. Zu breit ist das volle Spektrum an bekannten Katalysatorsystemen, von denen sich andererseits nur eine bescheidene Auswahl wirklich dauerhaft in Forschung und Produktion durchsetzen kann. Im Folgenden soll deshalb eine Fokussierung auf die Phosphine erfolgen. Von allen in der Pd-Katalyse bekannten Liganden sind Phosphine die am häufigsten verwendeten. Ligandeneigenschaften der Phosphine sind vergleichsweise gut untersucht und bei Katalysen im technischen Maßstab erhalten Pd-Phosphinkomplexe, wie im Verlauf dieser Arbeit noch gezeigt wird, in der Regel den Vorzug. Gleichwohl ist das Entwicklungspotential neuer Phosphine längst nicht ausgeschöpft, wie der folgende Streifzug durch die Literatur demonstriert.

1.2. Leistungsstarke Phosphinliganden in Pd-katalysierten Kupplungsreaktionen

Wie bereits eingangs erwähnt, ist Triphenylphosphin ***der*** Ligand für Pd-katalysierte Kupplungsreaktionen schlechthin. Mit Triphenylphosphin begann die Ära der Pd-vermittelten Kreuzkupplungen. Obwohl *Heck* bereits 1983 mit der Verwendung von Tri-*ortho*-tolylphosphin den positiven Einfluss höherer sterischer Belastung des Phosphorzentrums auf die katalytische Aktivität erkannte,[102] blieb Triphenylphosphin trotz der begrenzten katalytischen Aktivität seiner Palladium-Triphenylphosphinkomplexe ein Standardligand. Später berichteten *Herrmann* und *Beller* von der hervorragenden katalytischen Aktivität des dimeren Komplexes $Pd_2(P(o\text{-}Tol)_3)_2(OAc)_2$, der sich aus Palladiumacetat und Tri-

ortho-tolylphosphin synthetisieren lässt, und setzen damit einen Meilenstein in der Palladiumkatalyse.[103] Die Umsetzung der preiswerten und gut zugänglichen Chloraromaten auf breiter Linie war allerdings noch immer nicht möglich. Die Katalysatorkomplexe wiesen nicht die nötige Nucleophilie auf, um oxidativ in die intrinsisch stärkere C-Cl-Bindung zu insertieren. Zur katalytischen Aktivierung von Chloraromaten war somit ein Paradigmenwechsel in der Ligandenforschung notwendig. Anfang der 1990er Jahre begann man verstärkt, sterisch anspruchsvollere und elektronenreichere Trialkylphosphine anstelle der bislang vorherrschenden Triarylphosphine als Liganden in der Palladiumkatalyse einzusetzen. Infolge dessen gelang die Entwicklung zahlreicher leistungsstarker Phosphinliganden für Pd-vermittelte Kreuzkupplungsreaktionen.

1.2.1. Monophosphine

Ein entscheidender Durchbruch für die Steigerung der katalytischen Aktivität von Pd-Komplexen, vor allem auch für den erfolgreichen Einsatz schwieriger Kupplungssubstrate, erfolgte 1989 durch *Osborn*.[104] Ihm gelang die erfolgreiche Carbonylierung von Chlorbenzol unter Einsatz eines Pd-Komplexes mit Tricyclohexylphosphin (**M1**) als elektronenreichen, sterisch anspruchsvollen Trialkylphosphin-Liganden (Abb. 2).

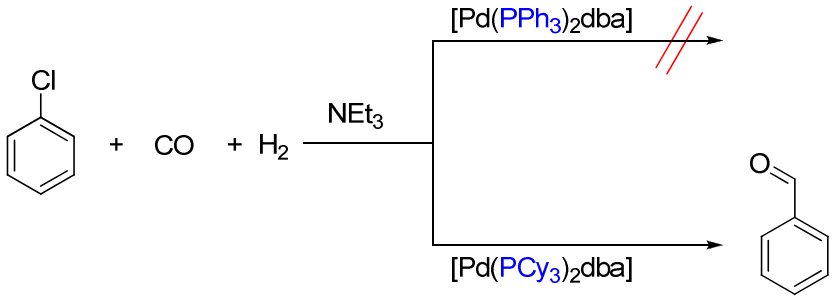


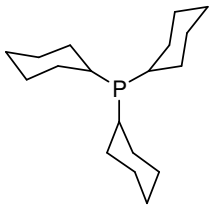
Abbildung 2. Carbonylierung von Chlorbenzol mit Pd/PCy_3-Komplexen.

In den folgenden Jahren etablierte sich Tricyclohexylphosphin als effizienter Ligand für den Einsatz in Carbonylierungs-[105] und Suzuki-Reaktionen[106] von Chloraromaten. Allgemeingültige Prognosen über Aktivitäten eines Katalysators sind, wie im Folgenden aufgezeigt, nur bedingt möglich; dies erschwert die systematische Entwicklung neuer Katalysatoren. So fanden *Plenio* und *an der Heiden* im Rahmen eines umfassenden Katalysatorscreenings für die Sonogashira-Kupplung, dass Pd-Komplexe mit Tri*iso*propylphosphin (**M2**) trotz ähnlicher sterischer und elektronischer Eigenschaften höhere katalyti-

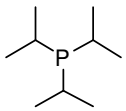
sche Aktivität aufweisen als diejenigen mit PCy_3.[107] Interessanterweise beobachteten *Fu* und Mitarbeiter für Pd-Komplexe mit Tricyclopentylphosphin (**M3**) oder **M2** in der Suzuki-Reaktion von Alkylchloriden signifikant geringere Aktivitäten als bei PCy_3.[108]

Tri*tert*butylphosphin

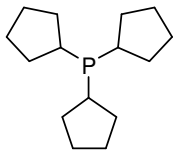
Eine weitere Steigerung der katalytischen Aktivität konnte *Fu* Mitte der 1990er Jahre infolge der Verwendung des sterisch noch anspruchsvolleren Liganden P*t*Bu_3 (**M4**) bewirken. Diese in der Praxis gewonnene Erfahrung steht im Einklang mit *Hartwigs* Erkenntnissen aus mechanistischen Untersuchungen,[109] dass der wachsende sterische Anspruch des Liganden den Schritt der reduktiven Eliminierung begünstigt.



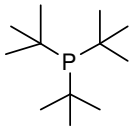
M1



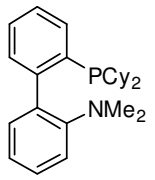
M2



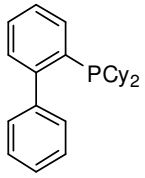
M3



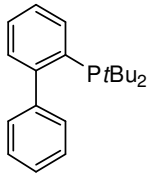
M4



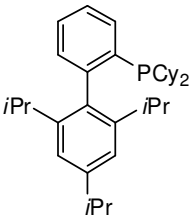
M5
DavePhos
Buchwald et al.



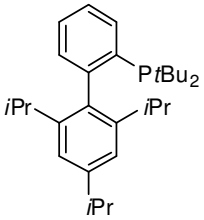
M6
CyclohexylJohnPhos
Buchwald et al.



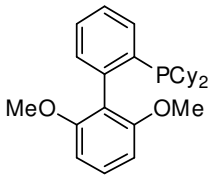
M7
JohnPhos
Buchwald et al.



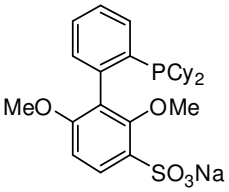
M8
XPhos
Buchwald et al.



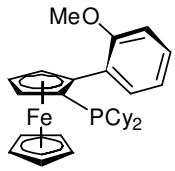
M9
***tert*-Butyl XPhos**
Buchwald et al.



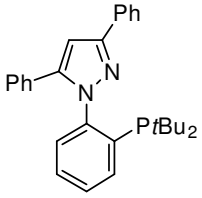
M10
SPhos
Buchwald et al.



M11
SPhos (water soluble)
Buchwald et al.

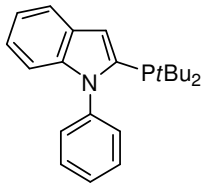


M12
MOPF
Johannsen et al.

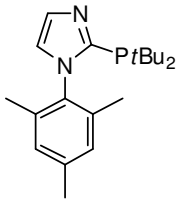


M13

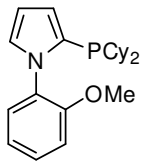
Singer et al.



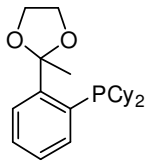
M14
cataCXium PIntB
Beller et al.



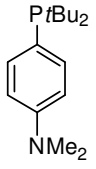
M15
cataCXium PIB
Beller et al.



M16
cataCXium POMeCy
Beller et al.

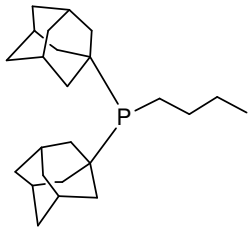


M17
Symphos
Guram et al.

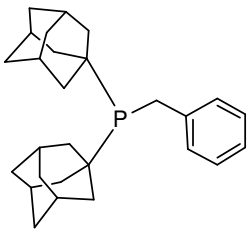


M18

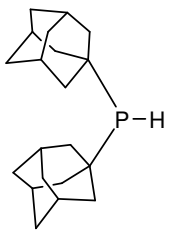
Guram et al.



M19
cataCXium A
Beller et al.

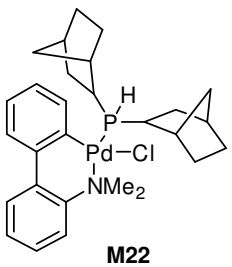


M20
cataCXium ABn
Beller et al. / Plenio et al.

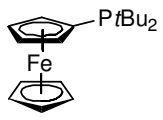


M21

Studer et al.

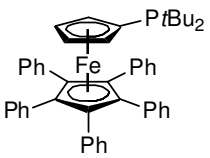


M22
SK-CC01-A
Studer et al.



M23

Hartwig et al.



M24
Q-Phos
Hartwig et al.

Abbildung 3. Wichtige Monophosphinliganden für C-C-Kreuzkupplungsreaktionen.

P*t*Bu$_3$ (**M4**) war synthetisch lange Zeit nur unzufriedenstellend zugänglich. Aufgrund der sterischen Hinderung ist über die klassische Grignardreaktion von überschüssigem *tert*-Butylmagnesiumchlorid mit Phosphortrichlorid nur die Vorstufe Di-*tert*-butylchlorphosphin zugänglich. Anschließende Umsetzung von Di-*tert*-butylchlorphosphin mit der reaktiveren Organolithiumverbindung *tert*-Butyllithium liefert das gewünschte **M4** nach *Hoffmann* und *Schellenbeck* in einer bescheidenen Gesamtausbeute von 17 % (Abb. 4).[110]

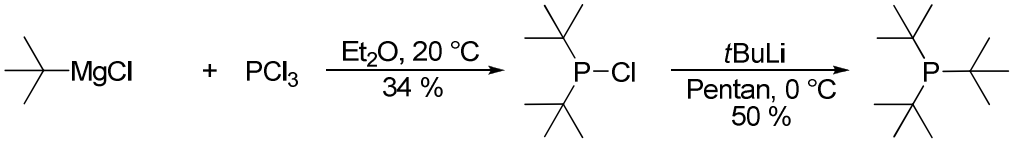


*Abbildung 4. Klassische Synthese von **M4** nach Hoffmann und Schellenbeck.*

In der Patentliteratur sind 2003 zwei ähnliche, jedoch unabhängig voneinander entwickelte Syntheserouten beschrieben, die einen wesentlich besseren Zugang zu P*t*Bu$_3$ unter Vermeidung teurer und gefährlicher Organolithiumverbindungen eröffnen.[111, 112] Ausgehend von *tert*-Butylmagnesiumchlorid und PCl$_3$ bzw. Di-*tert*-butylchlorphosphin gelang Forschern der Chemiekonzerne *Bayer* und *Hokko* die effiziente Darstellung von **M4** im industriellen Maßstab unter Einsatz katalytischer Mengen an Kupfer$^{I/II}$- und ggf. Lithium-Salzen (Abb. 5).

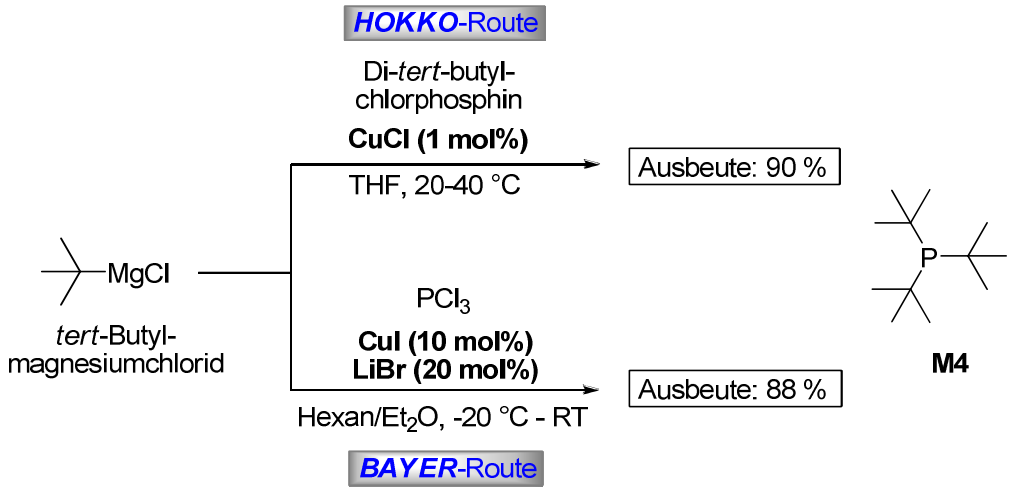


*Abbildung 5. Industrielle Synthese von **M4**.*

In den letzten Jahren entwickelte sich P*t*Bu$_3$ zu einem der Standardliganden im Bereich hochaktiver Monophosphine. Beispielhaft hierfür stehe das von *Fu* und *Littke* erarbeitete Reaktionsprotokoll für Pd/P*t*Bu$_3$ vermittelte Heck-Kupplungen von Arylchloriden.[113, 114] Der Einsatz von **M4** ermöglicht weiterhin die Verwendung von Arylchloriden,[115] z.B. bei der Buchwald-Hartwig-Aminierung zur Synthese von Triarylaminen,[116] bei Suzuki-Reaktionen[117, 118] oder die Verwendung von Arylbromiden in Sonogashira-Reaktionen bei Raumtemperatur.[119] Im Bereich der Stille-Kupplungen gelang *Fu et al.* die Entwicklung eines sehr vielseitigen Kupplungsprotokolls auf Basis des Liganden P*t*Bu$_3$. Dieses ermöglicht die Umsetzung nichtaktivierter Aryl- und Vinylchloride auch bei sterischer Hinderung sowie die Kupplung von Arylbromiden bei Raumtemperatur.[38] Für die von *Iizuka* und *Kondo* entwickelten Alkinylcarbonylierungen (Abb. 6) eignet sich Pd/**M4** auch bei niedrigen Reaktionstemperaturen hervorragend.[120]

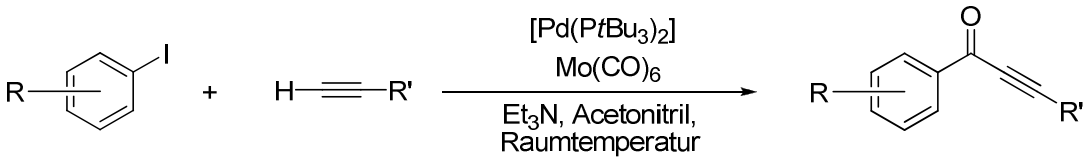


*Abbildung 6. Pd/**M4** katalysierte Alkinylcarbonylierung.*

Die hohe katalytische Aktivität der Pd/**M4**-Komplexe ermöglicht auch die Umsetzung von Chloraromaten im Rahmen von *α*-Arylierungsreaktionen von Estern. *Hartwig* und *Hama* berichteten kürzlich über die Entwicklung eines entsprechenden Reaktionsprotokolls, mit dem sich die als Enolate thermisch labilen Ester sehr effizient bei Raumtemperatur und niedriger Katalysatorbeladung umsetzen lassen.[121] Entgegen dem allgemeinen Trend für palladiumkatalysierte Prozesse war in diesen Arylierungsreaktionen mit Pd/**M4** ein niedrigerer Umsatz bei aktivierten als bei elektronenreichen Halogenaromaten zu beobachten.

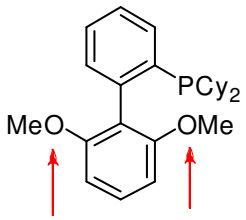
Ein Übersichtsartikel von *Brunel* gibt umfassende Einsicht in die Verwendung von **M4** als Ligand in Pd-katalysierten Kreuzkupplungsreaktionen.[122]

Biarylphosphine des Buchwald-Typs

Gegen Ende der 1990er Jahre wurde eine erstaunlich große Anzahl hochaktiver Liganden neu entwickelt. Inspiriert von dem von *Takaya* synthetisierten Bidentatliganden 2,2'-Bis(dicyclohexylphosphenyl)-1,1'-binaphthyl[123] entwickelte *Buchwald* mit seinen Mitarbei-

tern im Jahr 1998 den Biphenylaminophosphinliganden **M5** (DavePhos). Dessen zu diesem Zeitpunkt beispiellose katalytische Aktivität in Aminierungen und Suzuki-Reaktionen bei Raumtemperatur mit Arylchloriden führte *Buchwald* zunächst auf die hemilabil[124] chelatisierende Wirkung des Liganden zurück.[125] Die Notwendigkeit dieser Art Chelatstabilisierung wurde allerdings bald von *Buchwald* im Rahmen weiterer Forschungsarbeiten in Frage gestellt: Mit den einfacher zu synthetisierenden Desaminoderivaten **M6** und **M7** seiner Biphenylligandenfamilie konnten in Suzuki-Kreuzkupplungen sogar noch bessere Ergebnisse erzielt werden als mit **M5**.[126] Bislang ist trotz vielfältiger Arbeiten nur wenig über die Hintergründe der besonderen katalytischen Eigenschaften der Pd-Komplexe der Buchwald-Ligandenfamilie bekannt. Gründe für die gute Aktivität scheinen sowohl im sterischen Anspruch und der Elektronendichte der Phosphine als auch in der koordinativen Stabilisierung des Palladiums durch den nicht phosphortragenden Phenylring bzw. die bei einigen Liganden dieses Typs vorhandenen koordinierenden Codonoreinheiten zu liegen.[127-129]

2004 gelang *Buchwald* durch „rationales Katalysatordesign“ die Entwicklung des SPhos-Liganden (**M10**).[130] Die Einführung von Methoxy-Funktionalitäten in die 2'- und 6'-Position des Biarylligandengerüsts sollte nach Aussage von *Buchwald* mindestens vier positive Effekte mit sich bringen (Abb. 7):



M10

Effekte der Methoxy-Funktionalitäten:

- Stabilisierung des Pd-Komplexes durch freie e^--Paare am Sauerstoff
- Erhöhung der Elektronendichte im Biarylrückgrat
- Erhöhung der sterischen Belastung (OMe *vs*. H)
- Schutz vor Cyclometallierung

Abbildung 7. Rationales Ligandendesign der Buchwald-Liganden.[130]

1.) Durch die freien Elektronenpaare der Sauerstoffatome können sich hemilabile Chelate mit dem Pd-Zentrum ausbilden. Dies sollte die Stabilität des Katalysatorkomplexes und somit die Katalysatorlebensdauer positiv beeinflussen. 2.) Im Vergleich zum unsubstituierten Liganden bewirken die Methoxygruppen sowohl eine Erhöhung der sterischen Belastung als auch 3.) eine Erhöhung der Elektronendichte im Biarylrückgrat. 4.) Die Funktionalisierung der 2'- und 6'-Positionen schützt den Pd-Komplex vor CH-Aktivierung.[131] Die Ausbildung eines stabilen sechsgliedrigen Metallacyclus[132] bzw.

Bildung eines Phosphoniumsalzes aufgrund von reduktiver Eliminierung[133] sind Folgen solcher CH-Aktivierung und führen zur Deaktivierung des Katalysatorkomplexes.

Die Frage nach der Natur der hohen Aktivitäten von *Buchwalds* Biphenylphosphinliganden ist nicht nur von theoretischem Interesse; das Erkennen des Zusammenspiels der einzelnen Strukturelemente der Phosphine ist von großer Wichtigkeit für ein rationales Design noch besserer Liganden.[134] Bereits 2003 führten *Fink et al.* ^{31}P-NMR-Untersuchungen an Pd^0-Komplexen mit CyclohexylJohnPhos (**M6**) durch.[133] Bei NMR-Tieftemperaturmessungen beobachteten sie die Präsenz zweier diskreter P-Spezies und erhielten somit Hinweise auf eine Koordination des Pd mit dem distalen, also nicht phosphortragenden Arylring. Anhand der Daten aus Röntgenkristallstrukturanalysen von SPhos-Pd(dba)-Komplexen fand *Buchwald* 2005 einen weiteren deutlichen Hinweis auf eine eher unerwartet auftretende koordinative Stabilisierung des Pd-Zentralatoms durch den distalen Arylring (Abb. 9).[135]

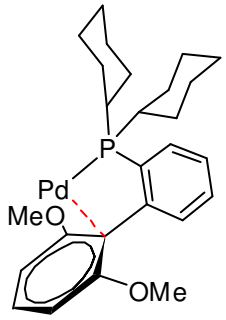


Abbildung 9. η^1-Koordination des distalen Arylrings

Der gefundene Abstand (Pd-C(*ipso*) = 237 pm) sowie Ergebnisse von Elektronendichteberechnungen lassen auf eine wie in Abbildung 9 gezeigte η^1-Koordination des Palladiumzentrums mit dem *ipso*-Kohlenstoffatom des distalen Arylrings schließen. Zur besseren Klärung dieses Sachverhalts berichtete *Barder* 2006 von Synthese und Untersuchung des in Abbildung 10 dargestellten Pd^I-Dimer-Komplexes mit dem Biarylmonophosphinliganden **M10**.[136] Anhand von Röntgenkristallstrukturanalysen und theoretischen Berechnungen fand *Barder* Hinweise auf zwei unterschiedliche Wechselwirkungen des nichtphosphortragenden Arylrings mit dem Palladiumzentrum:

a) In der gezeigten Struktur des Komplexes fällt gegenüber dem freien Phosphinliganden eine Vergrößerung des Bindungsabstands zwischen C(*ipso*) und C(*ortho*) sowie eine Verkürzung der Bindung O-C(*ortho*) auf. Diese Bindungsabstandsänderungen führt *Barder* auf eine elektrophile Addition des Pd-Zentrums an das *ipso*-Kohlenstoffatom über eine *σ*-Bindung und folgliche Ausbildung eines Areniumions zurück (Abb. 10, roter Teil). Zusätzliche Stabilisierung erfährt diese Bindung durch die in Mesomerie stehenden *ortho*-Methoxy-Gruppen. Die Stabilisierung des Areniumion-Intermediats ist somit ein wichtiges Indiz für die signifikant höhere katalytische Aktivität der Pd-Komplexe

von SPhos (**M10**) im Vergleich zu Pd-Komplexen von CyclohexylJohnPhos (**M6**), dem vergleichbaren Liganden ohne Methoxyeinheiten.

b) Der anhand der Kristallstruktur ermittelte und in Einklang mit den theoretischen Berechnungen stehende Bindungsabstand Pd-C(*para*) zwischen dem Pd-Zentralatom und dem nichtphosphintragenden Arylring beträgt analog zu der unter a) beschriebenen Bindung 219 pm. Die Bindungslängen innerhalb des oberen distalen Arylrings sind jedoch unverändert. Dies ist nach *Barder* Indiz für eine zweite Art der Stabilisierung über π-Wechselwirkungen (Abb. 10, blauer Teil).

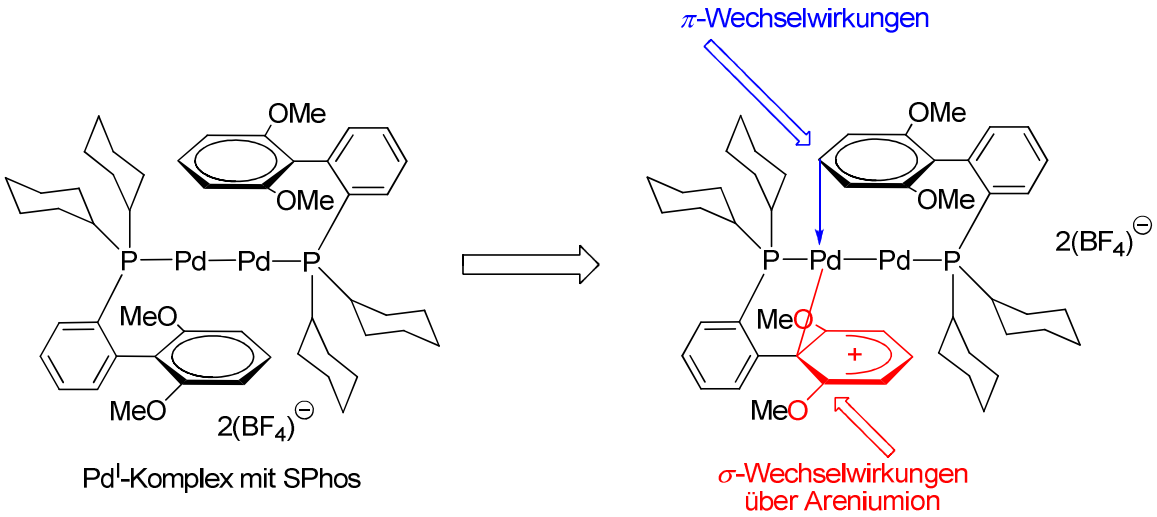


Abbildung 10. Gleichzeitige Stabilisierung des Pd-Zentrums über π- und σ-Wechselwirkungen mit dem nichtphosphintragenden Arylring.

Trotz vieler Untersuchungen sind somit Einfluss des distalen Arylrings und die genaue Natur der Koordination noch nicht vollständig verstanden. Vor allem gilt zu bedenken, dass die hier beschriebenen Wechselwirkungen eine signifikante Abhängigkeit von der Art des untersuchten Pd-Komplexes aufweisen. Daher lassen sich die Einflüsse der Liganden auf die im Katalysecyclus präsenten Spezies oft nur mit Einschränkungen untersuchen. Neuere, auf DFT-Rechnungen basierende Untersuchungen von *Buchwald et al.* aus dem Jahr 2007 deuten darauf hin, dass der distale Arylring auch im Katalysecyclus auftretende Zwischenstufen stabilisiert. Für die nach dem oxidativen Additionsschritt auftretende Pd^{II}-Spezies postulierte *Buchwald* koordinative Wechselwirkungen des Palladiumzentrums mit dem *ortho*-Kohlenstoff des distalen Arylrings sowie den freien Elektronenpaaren der beiden Methoxy-Funktionen.[128]

Nach *Buchwald et al.* ist die Wechselwirkung des distalen Arylrings mit dem Pd-Zentrum insbesondere für die Pd^0-Spezies im Katalysecyclus wichtig.[135] Die Aktivität des

Katalysators wird so in zweierlei Hinsicht vorteilhaft beeinflusst: Zum einen erleichtert die Wechselwirkung mit der Aryleinheit die Verschiebung des Gleichgewichts von Pd^0L_2 hin zur katalytisch aktiven monoligandierten Pd^0L_1-Spezies.[137] Zum anderen erfolgt durch das im Katalysecyclus vorliegende Gleichgewicht zwischen einem 12 bzw. 14 Elektronen-Palladiumzentrum eine Stabilisierung des Pd^0-Komplexes (Abb. 11). Dies vermindert die Bildung von Palladiumschwarz, welches sich leicht aus der instabilen niederkoordinierten Pd^0-Spezies bildet und zur Katalysatordeaktivierung führt.[138] Über die Natur und Bedeutung der Wechselwirkung des Palladiumzentrums mit dem Arylring für die anderen Pd-Spezies im Katalysecyclus ist bislang noch wenig bekannt.

Die Wechselwirkung des Pd-Katalysatorzentrums mit dem distalen Arylring beeinflusst folglich sowohl die katalytische Aktivität als auch die Langlebigkeit des Katalysators positiv.

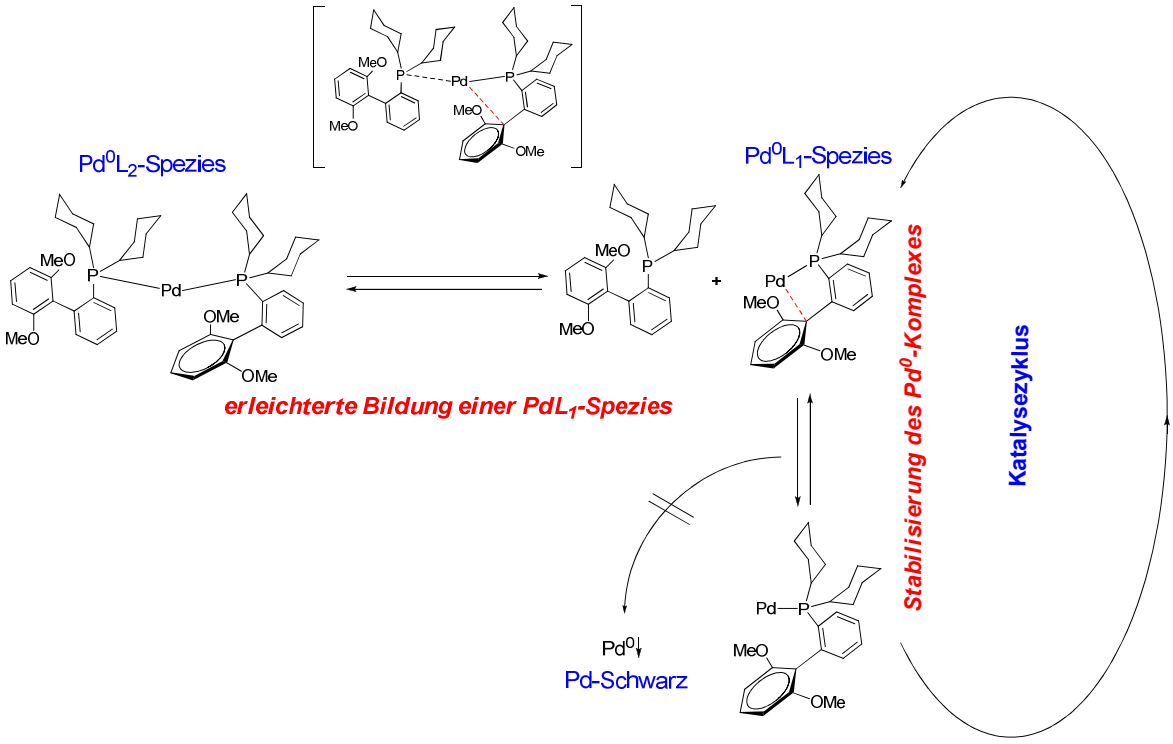


Abbildung 11. Stabilisierung der Pd-Komplexe mit Biphenylliganden in der Katalyse über Koordination mit dem distalen Arylring.

Mittlerweile ist eine Vielzahl verschiedener aktiver Biphenylphosphinliganden der Buchwald-Klasse bekannt.[139] Sterisch anspruchsvolle Buchwald-Liganden erwiesen sich als besonders aktiv in Suzuki-Kupplungen (Ligand **M8**)[140] oder Buchwald-Hartwig-Aminierungen bzw. -Veretherungen (Ligand **M9**)[141, 142] von Heteroarylchloriden. In Suzuki-Kreuzkupplungsreaktionen zeigten Pd-Komplexe mit SPhos (**M10**) bis dato ungekannt hohe

Aktivitäten. Pd/SPhos erreicht bei der Suzuki-Kupplung von Chloraromaten TON-Werte von 20000 und ermöglicht die Reaktion selbst deaktivierter Chloraromaten bei Raumtemperatur mit nur 0.5 mol% Katalysator (Abb. 8).

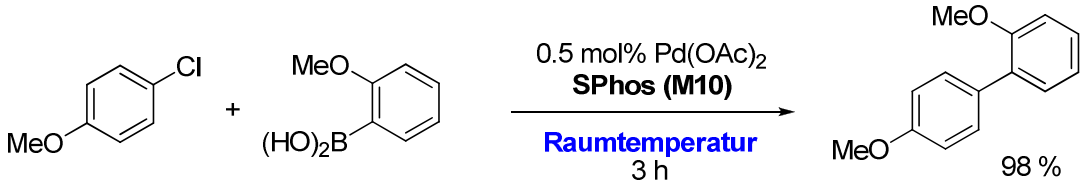


Abbildung 8. Pd/SPhos: Suzuki-Kreuzkupplung von Chloraromaten bei Raumtemperatur.[130]

Der sulfonierte Vertreter **M11** der Biphenyldialkylphosphinklasse ermöglicht Suzuki- und Sonogashira-Reaktionen mit Arylchloriden in purem Wasser bzw. wässrigen Lösemitteln.[143]

Die Synthese der Buchwald-Biphenylphosphine wurde mehrfach optimiert; mittlerweile ermöglicht ein optimiertes Syntheseprotokoll über eine Grignard-Route (Abb. 12) die Herstellung des Liganden in größerem Maßstab in akzeptabler Ausbeute (30-60 %).[144-146]

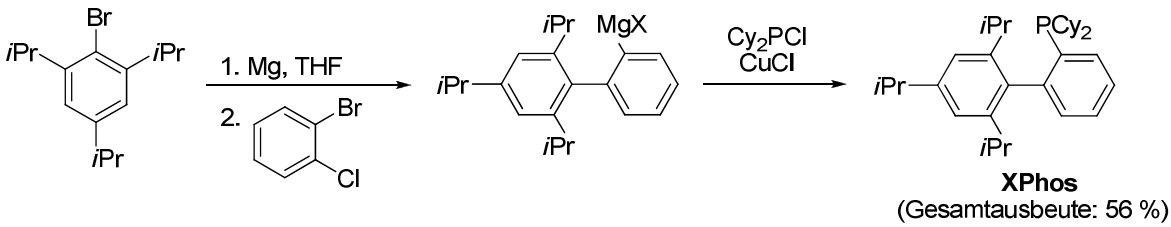


*Abbildung 12. Optimierte Route zur Synthese der Biphenylphosphine, hier am Beispiel XPhos (**M8**).*[146]

Auffällig ist die hohe Stabilität der Buchwald'schen Biphenylphosphine gegenüber Oxidation. JohnPhos (**M7**) beispielsweise weist eine Lagerstabilität von bis zu vier Jahren bei Aufbewahrung an der Luft bei Raumtemperatur auf.[147] Aufgrund praktischer und theoretischer Untersuchungen konnten *Buchwald* und *Barder* eine Interaktion des freien Elektronenpaars am Phosphor mit dem nichtphosphortragenden Arylring und einer darin begründeten Oxidationsinhibierung weitgehend ausschließen. Vielmehr scheint nahezu ausschließlich die sterische Belastung des Phosphinzentrums für die Oxidation von Aryldialkylphosphinen ausschlaggebend zu sein. Gestützt wird diese Annahme durch den praktischen Vergleich der Oxidationsneigung einer ganzen Reihe von Phosphinen. Abbildung 13 zeigt eine kleine Auswahl der Ergebnisse von *Buchwald* untersuchter Verbindungen.

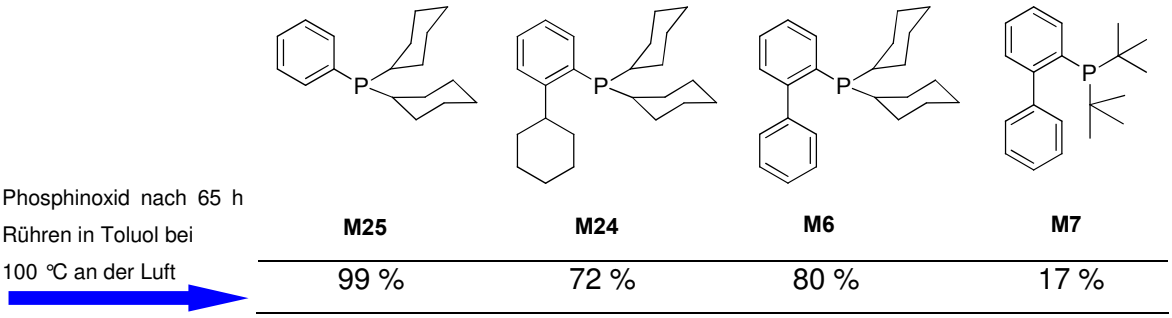


Abbildung 13. Oxidationsempfindlichkeit verschiedener Aryldialkylphosphine.[147]

Dicyclohexylphenylphosphin (**M25**) erweist sich aufgrund eines Arylsubstituenten am Phosphorzentrum bereits signifikant stabiler als Tricyclohexylphosphin. Dennoch liegt **M25** fast vollständig in Form seines Oxids vor, wenn es als Lösung in Toluol für 65 h bei 100 °C ohne Schutzgasatmosphäre gerührt wird. Wachsende sterische Belastung, z.B. in Form eines Biphenylrests (Ligand **M6**) oder des noch anspruchsvolleren Cyclohexylrests (Ligand **M24**) erhöht die Stabilität gegenüber Sauerstoff. Das sterisch sehr stark belastete JohnPhos (**M7**) lässt sich unter den angegebenen Bedingungen kaum noch zum Phosphinoxid oxidieren.

Mechanistisch begründen *Buchwald* und *Barder* die Stabilität der Biaryldialkylphosphine gegenüber Sauerstoff mit einer gehinderten Rotation des Dialkylphosphorzentrums (Abb. 14, hier am Beispiel von DicyclohexylJohnPhos (**M6**) demonstriert). Liegt das freie Elektronenpaar des Phosphorzentrums dem nichtphosphortragenden Arylrest zugewandt (*proximal*) vor (**M6-proximal**), kann zwar ein Sauerstoffdiradikal angreifen (**M6'-proximal**); aufgrund sterischer Hinderung ist jedoch die Annäherung eines zweiten Phosphinmoleküls nicht möglich, die Weiterreaktion zum Phosphinoxid (**M6-Oxid-proximal**) kann nicht stattfinden. Durch Rotation des Phosphorzentrums erhält das Elektronenpaar des Phospors jedoch freie Zugänglichkeit (**M6-distal**). Die Oxidation des Phosphins ist auf diesem Weg möglich.

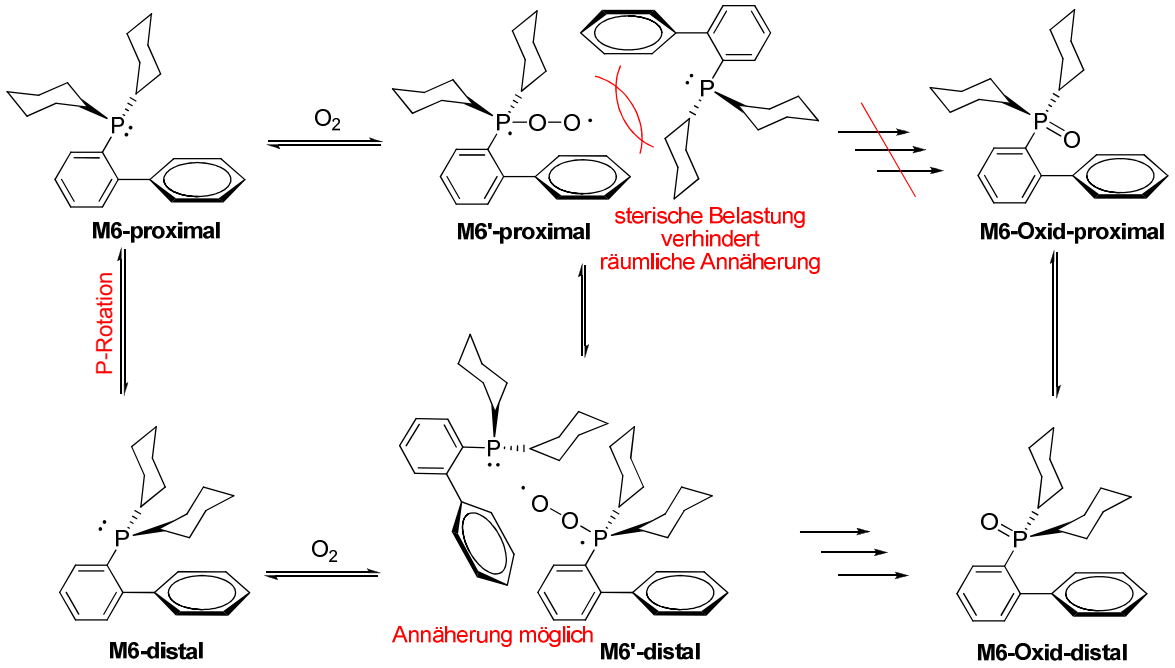
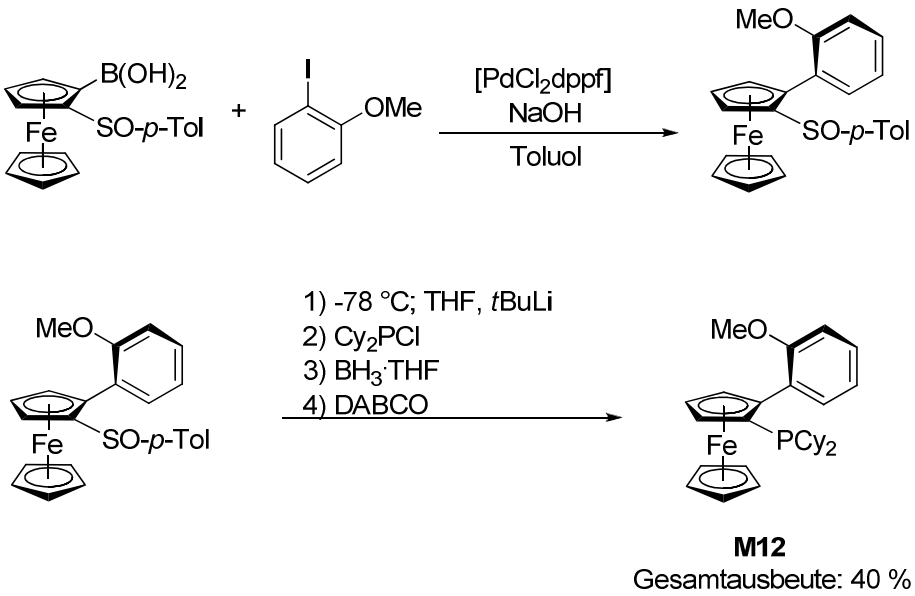


Abbildung 14. Postulierter Mechanismus zur Oxidation der Buchwald-Biphenyldialkylphosphine.

Trägt das Phosphorzentrum sterisch anspruchsvollere Substituenten als Cyclohexylreste, beispielsweise *tert*-Butylreste, ist eine Rotation des Phosphorzentrums hin zur distalen Konformation stark behindert. Dies erklärt die Oxidationsresistenz sehr sperriger Buchwald-Phosphine wie JohnPhos (**M7**) oder *tert*-ButylXPhos (**M9**).

Von Buchwald-Phosphinen abgeleitete Liganden

Mit den oxidationsunempfindlichen Arylmonophosphinoferrocenliganden (MOPF) entwickelten *Johannsen et al.* 2002 eine interessante Variation zu den Buchwald-Biarylphosphinliganden.[148, 149] Anstelle des phosphintragenden Arylrings besitzen die MOPF-Liganden ein Ferrocenyl-Rückgrat, das sowohl die Elektronendichte als auch den sterischen Anspruch der Phosphinfunktionalität erhöht. Palladiumkomplexe des elektronenreichen MOPF-Liganden **M12** erlauben Suzuki-Kupplungen mit nicht aktivierten Arylchloriden bei Raumtemperatur, die katalytische Aktivität reicht jedoch nicht an die der Buchwald-Liganden heran. Die planare Chiralität von **M12** im Ferrocenrückgrat ermöglicht zusätzlich auch asymmetrische Suzuki-Kupplungen. Die Ligandsynthese erfolgt wie in Abbildung 15 gezeigt in zwei Schritten:



M12
Gesamtausbeute: 40 %

*Abbildung 15. Synthese des MOPF-Liganden **M12**.*

Nach einer Suzuki-Arylierung der planar-chiralen Ferrocenylboronsäure lässt sich durch Reaktion mit *t*BuLi das enantiomerenreine Ferrocenylanion gewinnen. Anschließende Umsetzung mit Dicyclohexylchlorphosphin, Bildung des BH_3-Addukts und Aufarbeitung ergibt nach *Johannsen* **M12** in 40 %iger Ausbeute.[150]

Die gute Verfügbarkeit eines Liganden im Multikilogramm-Maßstab ist für industrielle Anwendungen von essentieller Natur. Folglich entwickelte die Katalyseabteilung des Pharmakonzerns Pfizer, USA, unter *Singer*, einem Schüler *Buchwalds*, die den Buchwald-liganden strukturell ähnlichen, aber deutlich leichter synthetisierbaren Phenylpyrrol- und Phenylpyrazol-Phosphinliganden, z.B. Ligand **M13**. Diese übertreffen zwar nicht die katalytische Aktivität der Buchwald-Biphenyl-Liganden in Aminierungsreaktionen, verfügen jedoch über außerordentliche Variabilität sowie gute Zugänglichkeit.[151-154] Ausgehend von *o*-Bromanilin bzw. *o*-Bromphenylhydrazin lassen sich die entsprechenden Bromphenylpyrrole und -pyrazole sehr leicht in guten Ausbeuten durch Kondensation mit Dionen synthetisieren. Die Phosphine sind durch Lithiierung der Brompyrrole bzw. -pyrazole mit *n*-Butyllithium und anschließender Reaktion mit Dialkylchlorphosphinen zugänglich (Abb. 16).[151]

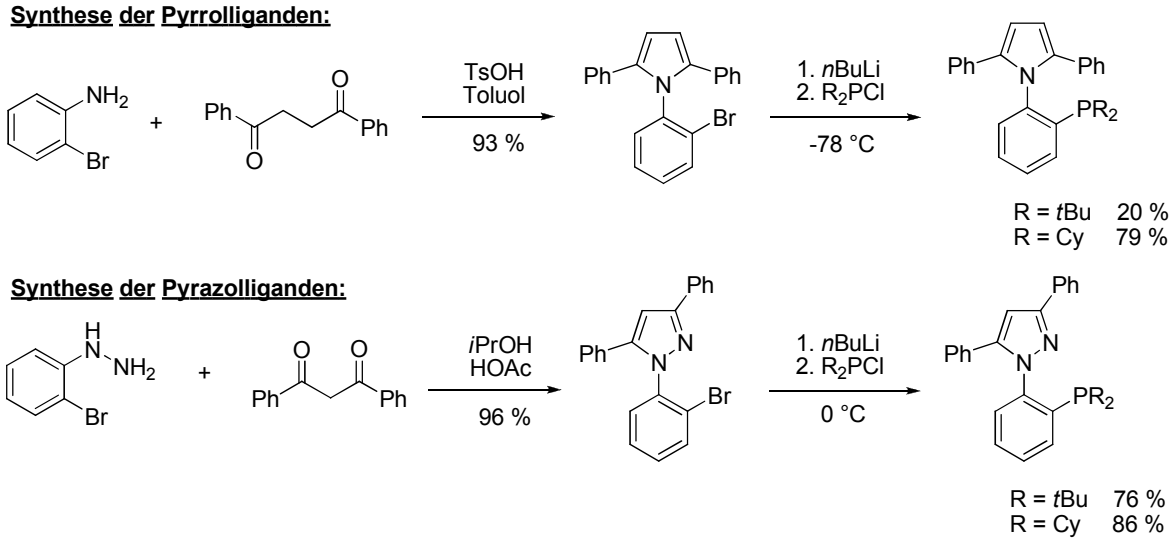


Abbildung 16. Synthese der Singer-Liganden.

Durch eine interessante Modifikation der Buchwald- bzw. Singer-Liganden gelang *Beller et al.* mit den 2-Phosphino-*N*-arylpyrrolen die Entwicklung einer leicht synthetisierbaren, variablen und zugleich hochaktive Pd-Komplexe bildenden Ligandenfamilie.[155][156-158] Die Synthese des Ligandgerüsts erfolgt zunächst über eine effiziente kupferkatalysierte *N*-Arylierung der entsprechenden Pyrrole (Indole, Pyrazole). Mittels einer *ortho*-Lithiierung in *α*-Position zum Stickstoffdonor gelingt anschließend die selektive Einführung der Dialkylphosphinofunktionalität. Stellvertretend für die Beller-Liganden des Pyrrol-Typs ist in Abbildung 17 die Synthese von cataCXium® PIntB dargestellt. Besondere Attraktivität weisen die Pyrrolliganden des Beller-Typs im Vergleich zu den Singer-Liganden unter anderem dadurch auf, dass die nötigen Ausgangsmaterialien auch für höher funktionalisierte Vertreter preiswert und kommerziell verfügbar sind. Mit diesen Liganden gelang es *Beller* auf hervorragende Art und Weise, die guten katalytischen Eigenschaften von *Buchwalds* Biphenylphosphinen mit sehr guter synthetischer Zugänglichkeit zu vereinen.

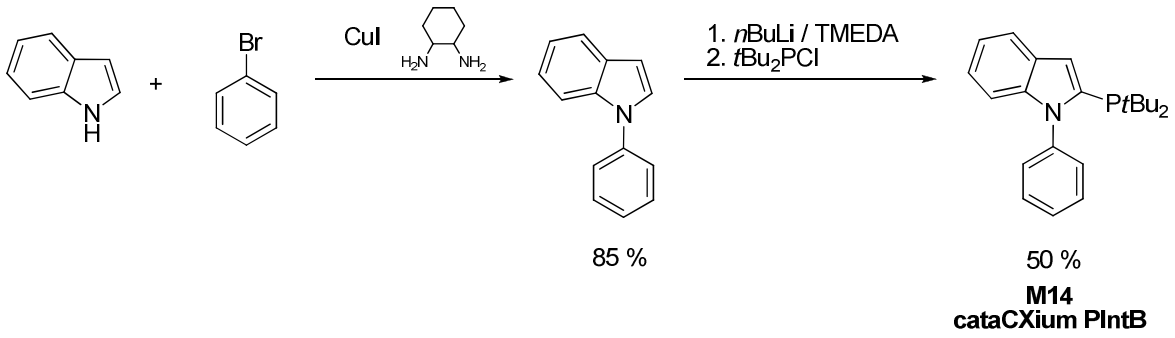


Abbildung 17. Synthese der Beller-Pyrrolliganden am Beispiel cataCXium® PIntB.

Insbesondere sterisch anspruchsvolle Vertreter dieser Klasse zeigen in Pd-Komplexen hervorragende katalytische Eigenschaften in der Buchwald-Hartwig-Aminierung von Arylchloriden (TON = 8000 beim Umsatz von 3-Chlortoluol mit *N*-Methylanilin mit Ligand **M14**,[159] Aminierungen mit Chloraromaten bei Raumtemperatur mit Ligand **M15** (0.5 mol% Pd-Beladung)) (siehe Abbildung 18).[160]

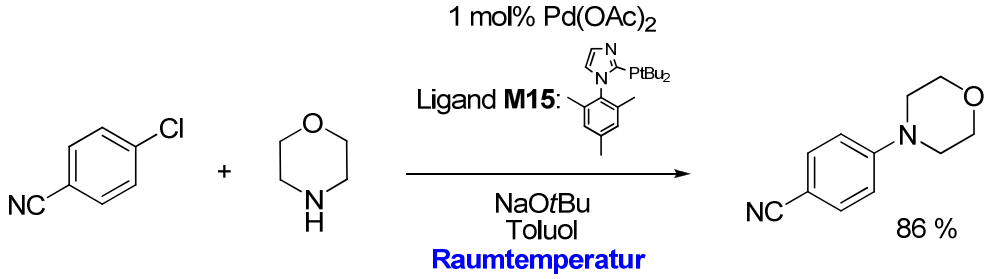


Abbildung 18. Pd-katalysierte Aminierung von Chloraromaten bei Raumtemperatur.

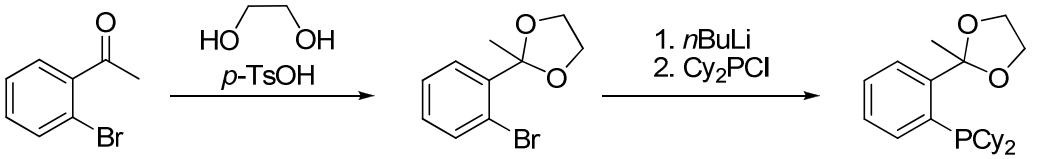
Der sterisch anspruchsvolle Pyrrolligand **M14** setzt bei Buchwald-Hartwig-Veretherungen von Arylchloriden (bis zu TON = 1000) Maßstäbe.[161] Für die Veretherung elektronenreicher Bromindole zeigte sich überraschenderweise *N*-Phenyl-2-(di-1-adamantylphosphino)-pyrrol als Ligand der Wahl und zahlreichen anderen hochaktiven Liganden des Buchwald-Typs, aber auch vielen vom Buchwald-Typ abgeleiteten Phosphinen überlegen.[162] Kürzlich gelang es *Beller et al.*, Pd/**M14**-Komplexe als hocheffiziente Katalysatoren für Sonogashira-Kupplungen mit heterocyclischen Substraten zu etablieren und so daran zu erinnern, dass palladiumkatalysierte Kreuzkupplungen vielseitige und nachhaltige Synthesemöglichkeiten für pharmazeutisch interessante Substrate bieten.[163]

Ähnlich wie bei den Buchwald-Liganden können am nichtphosportragenden Aromatenteil der Pyrrolliganden weitere Funktionalitäten als Codonoren angebracht werden (z.B. eine Methoxygruppe, Ligand **M16**).[159] *Buchwalds* Thesen zur rationalen Ligandenoptimierung entsprechend[130] sollten diese Codonoren die katalytischen Eigenschaften ähnlich wie im Fall SPhos positiv beeinflussen. In der Tat zeigt **M16** in Aminierungsreaktionen eine signifikant bessere katalytische Aktivität als sein unsubstituiertes Analogon.[159] In einem direkten Vergleich der beiden Liganden im Rahmen einer Suzuki-Kupplung schnitt jedoch der mit **M16** gebildete Pd-Komplex schlechter ab als sein unsubstituierter Vorläufer.[156] Folglich bleibt an dieser Stelle weiterhin offen, ob die Erhöhung der katalytischen Aktivität durch Einführen bestimmter funktioneller Gruppen in einer koordinativen Stabilisierung des Pd-Zentrums oder schlicht in einer größeren sterischen Belastung begründet ist.

Sicher scheint indes die vorteilhafte Wirkung des Biarylsystems bei den Liganden von *Buchwald*, *Singer* und *Beller*.

Symphos

Das 1999 von *Guram et al.* im Symyx-Konzern entwickelte Aryldialkylphosphin Symphos (**M17**) lässt sich leicht und preiswert aus *p*-Bromacetophenon durch Acetalisierung der Ketofunktion mit Ethylenglykol und anschließender Reaktion des lithiierten Intermediates mit Dicyclohexylchlorphosphin synthetisieren (Abb. 19).[164]



p-Bromacetophenon — 97 % Ausbeute — 83 % Ausbeute **Symphos (M17)**

*Abbildung 19. Synthese von Symphos (**M17**).*

Symphos weist bei Suzuki-Kupplungen oder Aminierungsreaktionen mit Arylchloriden eine etwa 10-100fach niedrigere Aktivität auf als die entsprechenden Biarylphosphinliganden, obwohl auch **M17** über hemilabil chelatisierende, stabilisierend wirkende Alkoxyfunktionalitäten (P,O-Ligand) verfügt.[164-166] In gleicher Größenordnung bezüglich der Aktivität liegen auch einfache Aryldialkylphosphine wie **M18**, welche luftstabile Pd-Komplexe bilden, die sich als gute Katalysatoren für Suzuki-Reaktionen mit Heteroarylchloriden erwiesen haben.[167, 168]

Um den Einfluss von Alkoxygruppen auf die katalytische Aktivität von Ligandensystemen näher zu untersuchen, sind die jeweils substituierten und unsubstituierten Liganden miteinander zu vergleichen. In Abbildung 20 sind die in der Literatur berichteten Aktivitäten der einzelnen Liganden in einer untereinander vergleichbaren Suzuki-Reaktion dargestellt. Während die Präsenz von Methoxygruppen bei den Buchwald-Systemen die Aktivität des Katalysators signifikant steigert, ist bei den strukturell verwandten Pyrrol-Liganden von *Beller* sogar eine Abnahme der katalytischen Aktivität durch Einführung einer Methoxyfunktion in *ortho*-Position am distalen Arylring zu beobachten.

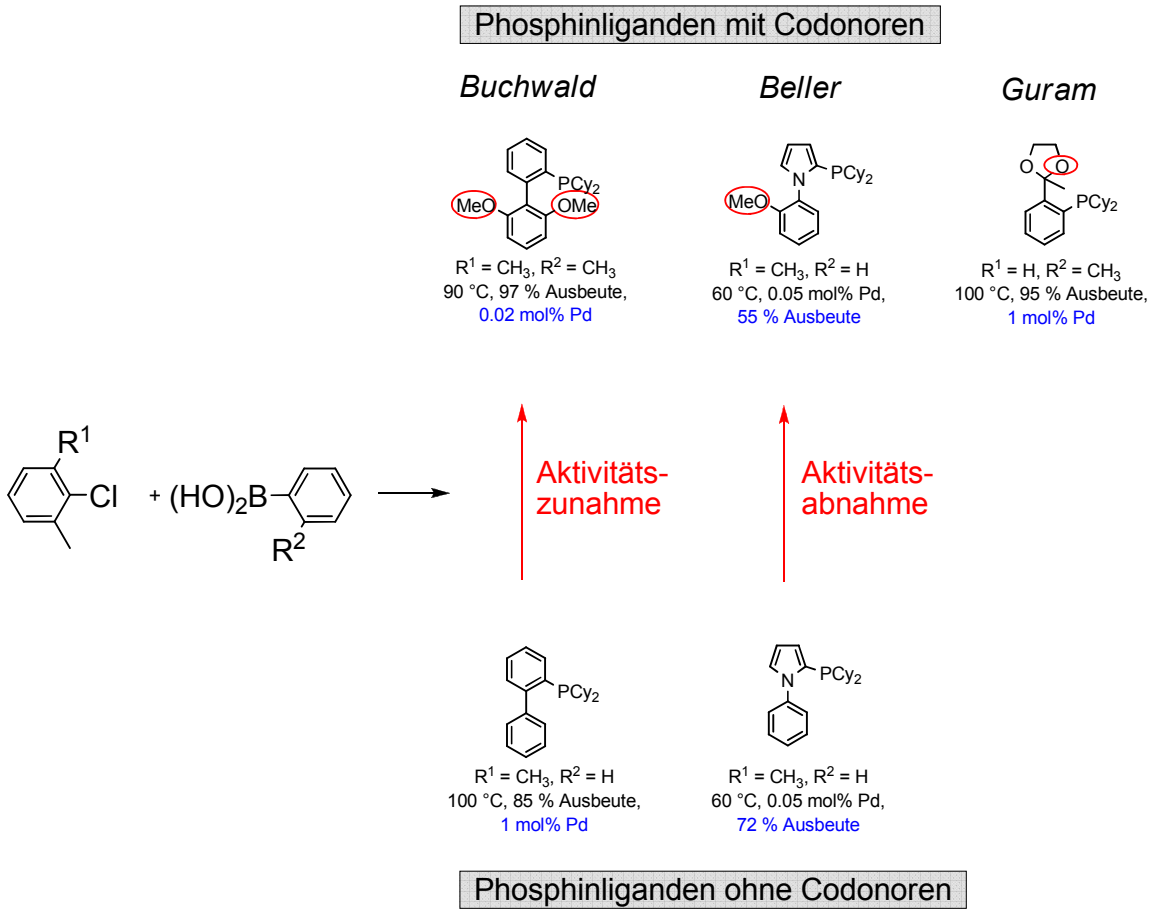


Abbildung 20. Einfluss von Alkoxysubstituenten auf die Katalysatoraktivität - Vergleich von Literaturaktivitäten.[126, 130, 156, 166]

Dies lässt den Schluss zu, dass eher sterische als koordinative Gründe für die Aktivitätssteigerung der Buchwald-Systeme verantwortlich sind. Viel wichtiger als eine stabilisierende Wirkung über Codonoreinheiten wie Methoxygruppen scheint die Präsenz eines Arylrings *ortho*-ständig zur Phosphinogruppe zu sein. Trotz annähernd vergleichbarer sterischer Belastung und vorhandenen Alkoxygruppen weist *Gurams* Symphos-Ligand in der Vergleichsreaktion eine deutlich niedrigere Reaktivität auf.

Ad_2PR-Serie

Im Jahr 2000 berichtete *Beller* von den hervorragenden Eigenschaften der Diadamantylalkylphosphine. Diese sind auch im technischen Maßstab mittels einer Phosphoniumsalzreaktion und anschließender Deprotonierung leicht und sauber synthetisierbar (Abb. 21).[13, 169, 170]

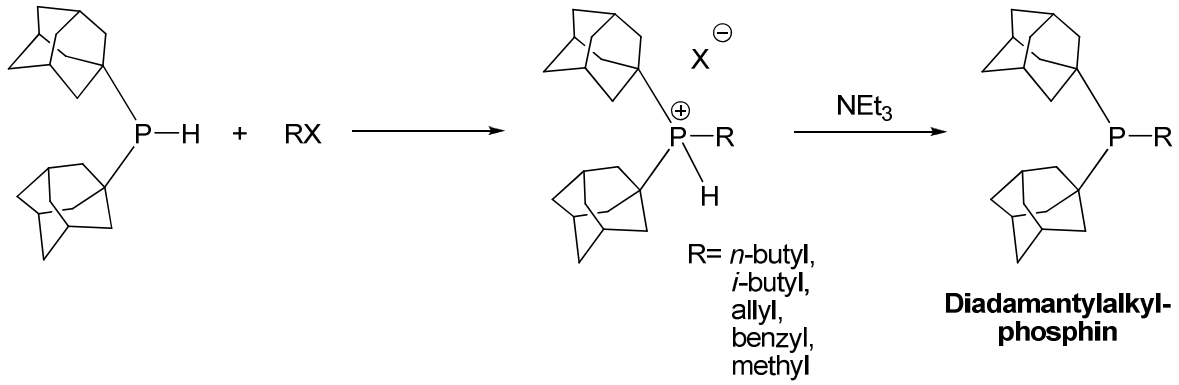


Abbildung 21. Synthese der Diadamantylalkylphosphine über eine Phosphoniumsalz-reaktion.

Das Intermediat Diadamantylphosphin lässt sich preiswert nach *Schmutzler* und *Goerlich* durch Reaktion von Adamantan mit Phosphortrichlorid unter Friedel-Crafts-Bedingungen und anschließender Reduktion mit Lithiumaluminiumhydrid in fast quantitativer Ausbeute synthetisieren (Abb. 22).[171]

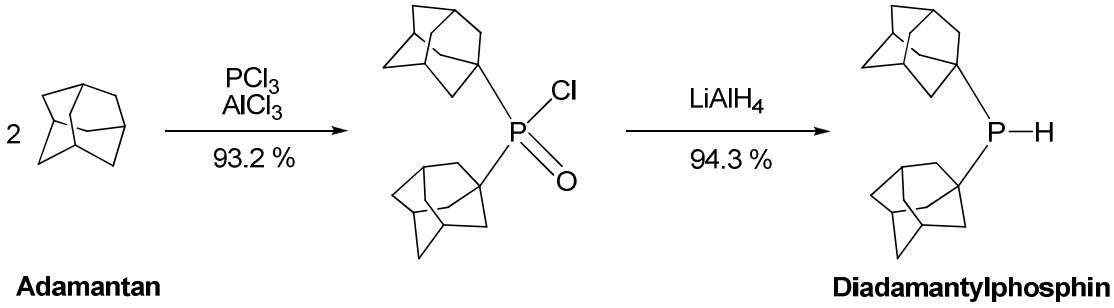


Abbildung 22. Synthese des Intermediats Diadamantylphosphin.

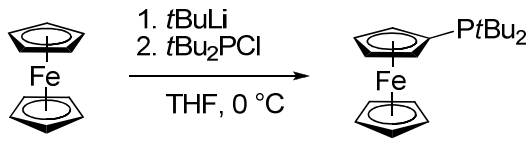
Der wohl prominenteste Vertreter dieser Ligandenklasse, Ad_2PnBu (**M19**),[172] stellt als Pd-Komplex einen Katalysator für Suzuki-Reaktionen mit Arylchloriden dar, dessen TON um den Faktor 2-3 höher ist als die von Komplexen mit $PtBu_3$ (**M4**) oder **M5**.[173] Pd-Komplexe mit **M19** wurden auch erfolgreich in Heck-Kupplungen,[13] Carbonylierungen,[174] Buchwald-Hartwig-Aminierungen,[175, 176] α-Arylierungen[42] oder erst kürzlich bei der Cyanierung[19, 177] von Arylchloriden eingesetzt. Carbonylierungen von Heteroarylbromiden zu wichtigen Intermediaten für Pharma und Feinchemie sind durch Ad_2PnBu (**M19**) bereits bei sehr niedrigen Drücken mit hoher Selektivität möglich.[174, 178, 179]

Für Sonogashira-Kupplungsreaktionen mit Arylchloriden und -bromiden berichteten *Plenio* und *Köllhofer* besonders hohe Aktivitäten für Pd-Komplexe mit dem von *Beller* erstmals beschriebenen Derivat Ad_2PBn (**M20**).[169, 180, 181]

Für Heck-Reaktionen mit Arylchloriden fanden *Studer et al.* von Solvias sterisch anspruchsvolle sekundäre Alkylphosphine wie etwa Ad_2PH (**M21**) als nahezu genauso aktive Liganden wie Trialkylphosphine, z.B. P*t*Bu_3 (**M4**).[182] In Kombination mit Stickstoffpalladacyclen ergeben sich mit sekundären Phosphinen interessante Katalysatorkomplexe für Suzuki-Kupplungen oder Aminierungen von Arylchloriden, deren Aktivitäten z.T. mit der von Pd/**M4** vergleichbar sind.[183, 184] Komplex **M22** sei an dieser Stelle als Beispiel für einen der aktivsten Vertreter dieser Klasse genannt.

Q-Phos

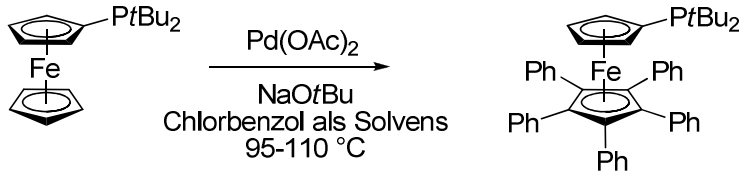
1999 berichtete *Hartwig* als erster, dass auch Monophosphinliganden mit einem Ferrocenylrückgrat, z.B. Fc*t*Bu_2 (**M23**) die Buchwald-Hartwig-Veretherung mit Arylchloriden ermöglichen.[185] Aufgrund der großen sterischen Belastung des Phosphins erfolgt die Synthese ähnlich wie bei P*t*Bu_3 über die Umsetzung eines entsprechenden Chlorphosphins mit einem ausreichend reaktiven Lithiumorganyl. Die Synthese des Phosphins **M23** gelingt durch Lithiierung von Ferrocen mit *t*BuLi und anschließender Reaktion mit Di*tert*-butylchlorphosphin in 85 %iger Ausbeute (Abb. 23).[185] Bei der Synthese elektronenreicher monosubstituierter Ferrocenylliganden im technischen Maßstab stellen Verunreinigungen durch disubstituierte Nebenprodukte oft ein Problem dar.[186]



Ferrocen **M23**

*Abbildung 23. Synthese von $FcPtBu_2$ (**M23**).*

Wenig später stellte sich heraus, dass sich Liganden wie **M23** unter bestimmten Bedingungen Pd-katalysiert am unteren, nichtphosphintragenden Ring wie in Abbildung 24 gezeigt selbst arylieren.[187]



M23 **M24**
Q-Phos

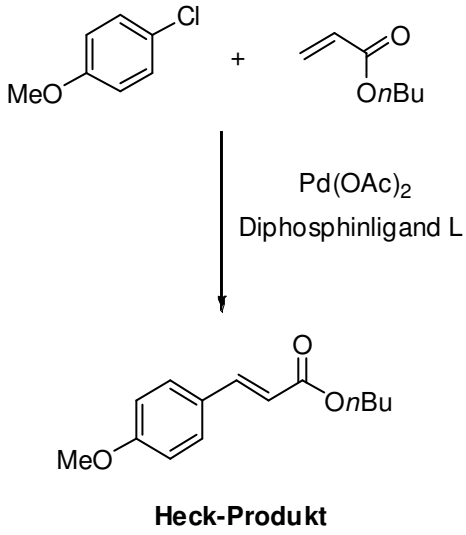
*Abbildung 24. Pd-katalysierte Autarylierung von $FcPtBu_2$ (**M23**).*

Die so vorliegenden pentaarylierten Liganden weisen aufgrund größerer sterischer Belastung signifikant höhere Aktivitäten auf. So ist z.B. das von *Hartwig* in Kooperation mit *Johnson Matthey* entwickelte luftstabile Q-Phos (**M24**) ein überaus aktiver Ligand für Buchwald-Hartwig-Veretherungen,[187] -Aminierungen, Suzuki-Kupplungen (auch mit Alkylboronsäuren unter milden Bedingungen)[188] oder *α*-Arylierungen.[44, 189] Erst kürzlich berichteten *Hartwig et al.* von erfolgreichen, bislang nur schwer möglichen *α*-Arylierungen an linearen Aldehyden mittels Pd/Q-Phos.[190]

1.2.2. Zweizähnige Phosphine

Zur Aktivierung von Chloraromaten in Formylierungs- und Carbonylierungsreaktionen fand *Milstein* 1989, dass Pd-Komplexe der Bidentatliganden DiPPP (**B5**) und DiPPB (**B6**) höhere katalytische Aktivität besitzen als die Monodentatliganden PPh_3 oder $P\textit{i}Pr_3$ (**M2**).[191, 192] *Milstein* führte die gute katalytische Aktivität auf eine höhere Stabilität der elektronenreichen Pd^0-Spezies infolge einer Chelatisierung zurück. **B5** und **B6** stellen auch aktive Liganden für die Heck-Olefinierung dar; die *E*/*Z*-Selektivität lässt sich über die Länge der Linker-Kette des Bidentatliganden beeinflussen.[193, 194] 1995 gelang *Herrmann, Beller et al.* die Aktivierung von Chloraromaten in der Heck-Olefinierung unter Einsatz preiswerter und leichter zugänglicher Diphosphindiarylliganden, z.B. **B1**-**B4** (DPPM, DPPE, DPPP, DPPB) (Abb. 25).[195]

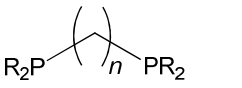
Während **B1**-**B3** aufgrund eines kleinen Bisswinkels sehr stabile Chelate mit Pd bilden, die jedoch nahezu inaktiv in der Heck-Reaktion mit Arylchloriden sind, steigt die katalytische Aktivität mit der Größe des Bisswinkels an. $Pd(DPPB)_2$-Komplexe oder Komplexe entsprechender Diphosphine mit noch längeren *n*-Alkyllinkern zeigen mit dem Bisswinkel ansteigende, gute Aktivitäten.



Heck-Produkt

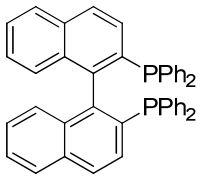
Ligand	Ausbeute Heck-Produkt [%]
DPPM (**B1**)	7
DPPE (**B2**)	21
DPPP (**B3**)	28
DPPB (**B4**)	38
DPPPent	38
DPPH	37

Abbildung 25. Einfluss des Bisswinkels auf die katalytische Aktivität: Heck-Kupplung von Chloraromaten.



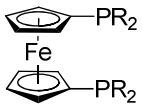
B1 *n* = 1; R = Ph; **DPPM**
B2 *n* = 2; R = Ph; **DPPE**
B3 *n* = 3; R = Ph; **DPPP**
B4 *n* = 4; R = Ph; **DPPB**

B5 *n* = 3; R = *i*Pr; **DiPPP**
B6 *n* = 4; R = *i*Pr; **DiPPB**

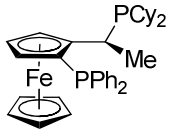


B7
BINAP

Noyori et al.

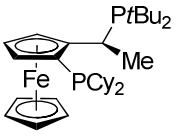


B8 R = Ph; **DPPF**
B9 R = *t*Bu; **D*t*BPF**



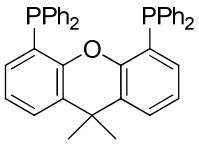
B10
Josiphos

Togni, Spindler et al.



B11

Hartwig et al.



B12
Xantphos

van Leeuwen et al.

Abbildung 26. Wichtige Polydentatphosphinliganden für C-C-Kreuzkupplungsreaktionen.

In umfangreichen Katalysator-Screenings zur Heck-Olefinierung fanden *Hartwig et al.*, dass bei der Kupplung von Bromaromaten Bidentatliganden generell hochaktiven Monodentatliganden unterlegen sind.[71] Bei der Kupplung von Chloraromaten konnte *Beller* interessanterweise eine signifikante Überlegenheit auch einfacher Diphosphine wie DPPB gegenüber hochaktiven Monophosphinen wie P*t*Bu$_3$ zeigen.[196] Aufgrund des hohen Bisswinkels stellt DPPB auch einen guten Liganden für die Buchwald-Hartwig-Aminierung dar.[197] Im Vergleich zu Monophosphinen verfügen Diphosphinkomplexe in der Regel über höhere Selektivitäten und Stabilitäten bei Aminierungsreaktionen.[198] Ein weiteres Beispiel dafür, dass zweizähnige Phosphine bisweilen herausragende Liganden in palladiumvermittelten Katalysen darstellen können, gab *Beller* 2007 mit einem Syntheseprotokoll zur Formylierung von Aryltriflaten mit Synthesegas. Hier erwies sich DPPP als der Ligand der Wahl, während andererseits hochaktive Monophosphinliganden wie Ad$_2$P*n*Bu (**M18**) den Diphosphinliganden signifikant unterlegen waren.[199]

BINAP

Als Ligand in C-N-Bindungsknüpfungsreaktionen besonders verbreitet ist das von *Noyori*[200] für enantioselektive Hydrierungen entwickelte Diphosphin BINAP[201] (**B7**). BINAP verfügt über einen großen Bisswinkel, ist in seiner racemischen Form preiswert, in großem Maßstab kommerziell verfügbar und in palladiumvermittelten Kreuzkupplungen signifikant katalytisch aktiver als Palladiumkomplexe von Triarylmonophosphinen.[48, 198, 202-204] Unter Verwendung von [Pd(BINAP)$_2$]-Komplexen gewannen *Hartwig et al.* sowie *Buchwald et al.* interessante mechanistische Einblicke in die Pd-katalysierte Aminierung.[205, 206] Technisch wurde BINAP zunächst über eine von *Noyori* entwickelte und vom japanischen Takasago-Konzern patentierte Route synthetisiert (Abb. 27).[207-209] Hierbei wird racemisches Binol zunächst selektiv mit Triphenylphosphindibromid bromiert, anschließend erfolgt die Kupplung von Diphenylphosphoroxychlorid unter Grignard-Bedingungen zur oxidierten Form des BINAPs (BINAPO). Dieses lässt sich im letzten Schritt mit Trichlorsilan zum BINAP reduzieren. Zur Gewinnung enantiomerenreinen BINAPs erfolgt auf der Stufe des BINAPO eine Enantiomerentrennung. Da für die überwältigende Mehrzahl der palladiumvermittelten Kreuzkupplungen jedoch BINAP in seiner racemischen Form völlig ausreichend ist, soll auf die Synthese von enantiomerenreinem BINAP im Rahmen dieser Arbeit nicht näher eingegangen werden.

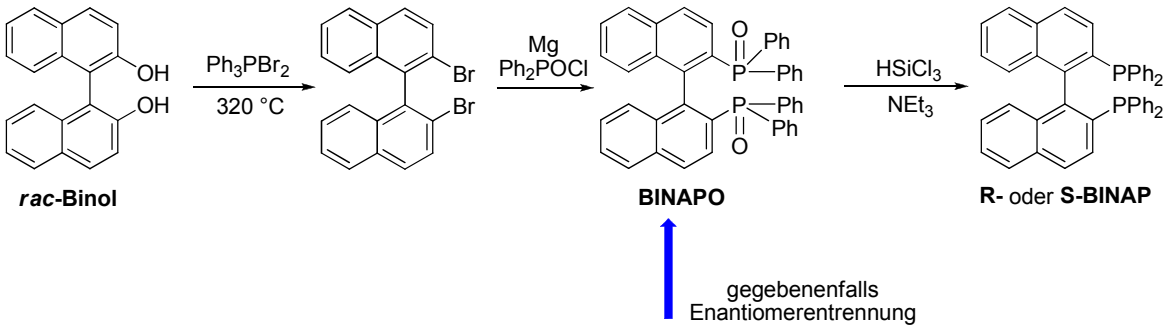


Abbildung 27. BINAP-Synthese nach der Takasago-Route.

Die Takasago-Route stellte sich an vielen Stellen als problematisch heraus. Deshalb wird BINAP in neuerer Zeit größtenteils auf anderen Synthesewegen dargestellt. Etabliert haben sich hierbei die Merck (USA)- und die Monsanto-Route. In beiden Fällen wird enantiomerenreines Binol mit Trifluormethansulfonsäureanhydrid verestert, um eine optimale Abgangsgruppe zu schaffen. Bei der Merck-Route[210] wird BINAP durch eine anschließende nickelkatalysierte Kreuzkupplung mit Diphenylphosphin erhalten (Abb. 28), die Monsanto-Route[211] führt nach Kupplung mit Diphenylchlorphosphin unter Negishi-Bedingungen zum gleichen Produkt (Abb. 29). Die Monsanto-Route erweist sich gegenüber der Merck-Route insofern als vorteilhaft, als dass Diphenylchlorphosphin im Gegensatz zu Diphenylposphin preiswert kommerziell verfügbar ist.

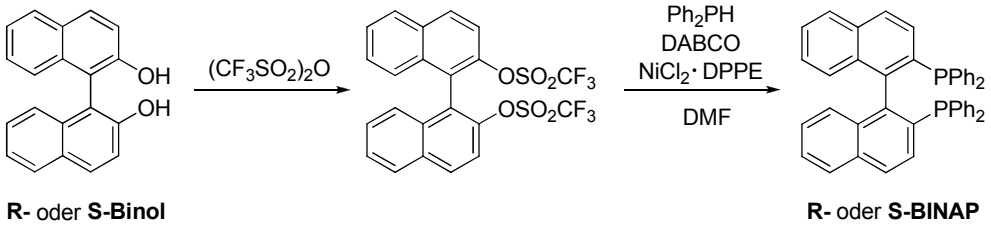


Abbildung 28. BINAP-Synthese nach der Merck (USA)-Route.

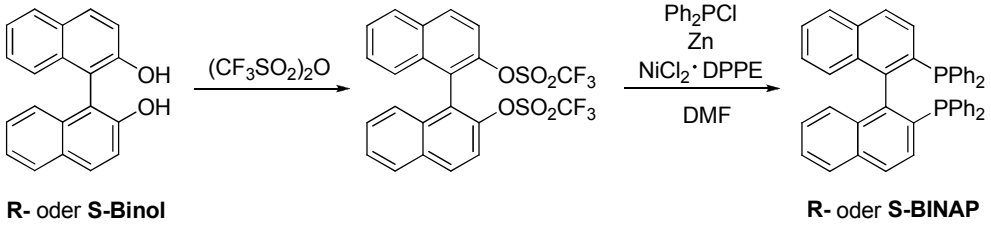


Abbildung 29. BINAP-Synthese nach der Monsanto-Route.

Ferrocenyldiphosphine

Eine weitere Diphosphinligandenklasse mit großem Bisswinkel stellen die Ferrocenylphosphine dar. Ferrocen lässt sich mit *n*BuLi in Verbindung mit TMEDA bequem in 1,1'-Position zweifach metallieren, das entsprechende Dilithioferrocen-TMEDA-Addukt ist sauber in nahezu quantitativen Ausbeuten isolierbar. Die Umsetzung des Dilithioorganyls mit Ph_2PCl bzw. tBu_2PCl führt zu den entsprechenden Ferrocenyldiphosphinen DPPF (**B8**)[186, 212, 213] oder D*t*BPF (**B9**)[186, 214] (Abb. 30).

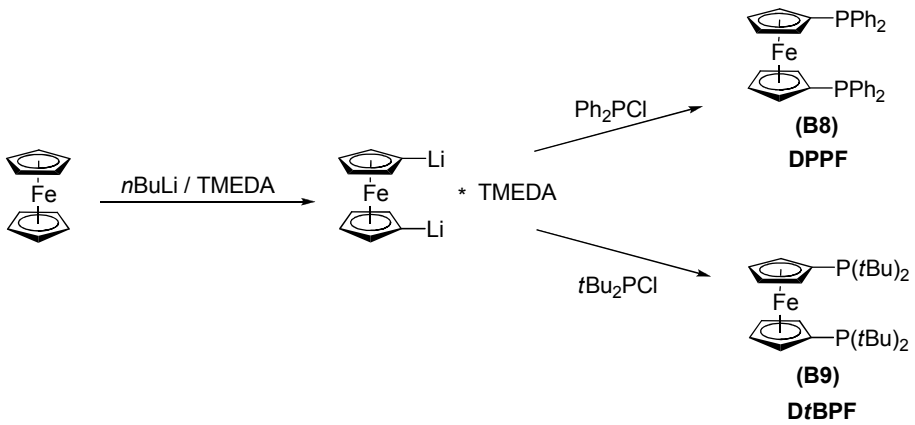


Abbildung 30. Synthese von DPPF und DtBPF.

Zusammen mit BINAP bezeichnete *Hartwig* diese aufgrund der guten Aktivität ihrer Palladium-Komplexe in Aminierungsreaktionen und der Fähigkeit der Aktivierung von Arylchloriden als sogenannte „2nd Generation Catalysts".[203] DPPF (**B8**) erwies sich als geeigneter Bidentatligand in diversen Aminierungs-[215, 216] oder Suzuki-Kupplungsreaktionen,[217, 218] bevorzugt unter Einsatz von Iod- und Bromaromaten. Für Kupplungen schwieriger Substrate wie Purine erwies sich DPPF sogar hochaktiven Monodentaten **M6** und **M7** der Johnphos-Klasse signifikant überlegen;[219] DPPF-Palladiumkomplexe finden in der industriellen Synthese des Pharmawirkstoffs Discodermolide® als Suzuki-Kreuzkupplungs-Katalysator Verwendung.[220]

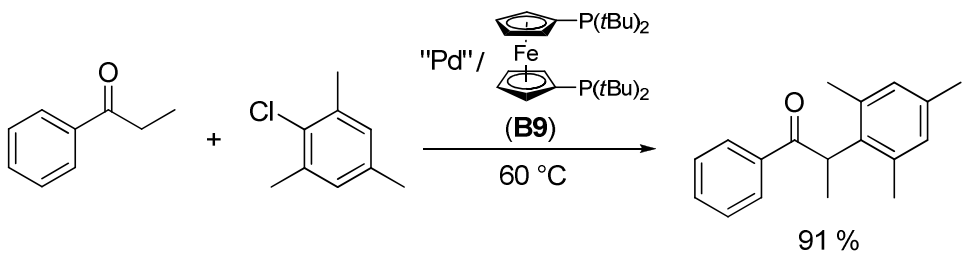


Abbildung 31. DtBPF: Effiziente α-Ketoarylierung von Arylchloriden.

Zur Aktivierung von Arylchloriden, z.B. in α-Keto-Arylierungen (Abb. 31) oder Suzuki-Reaktionen, erwies sich der sterisch anspruchsvollere D*t*BPF-Ligand (**B9**) als geeignet.[221, 222]

Die gute Aktivität der Bidentat-Phosphine des Josiphos-Typs (**B10**), die ebenfalls über ein Ferrocenyl-Rückgrat verfügen, führt man auf die Rigidität des Rückgrats, die sterische Belastung sowie den stark elektronendonierenden Charakter dieser Liganden zurück. Josiphos-Liganden sind in erster Linie im Bereich enantioselektiver Hydrierungen von Bedeutung.[223, 224] In Kreuzkupplungsreaktionen erwiesen sie sich für Thioethersynthesen mit Arylchloriden, -bromiden oder -sulfonaten,[57, 225] Carbonylierungen von Arylsulfonaten[226] in einigen Fällen als erste Wahl und z.T. einzähnigen Phosphinen des XPhos-Typs (**M8** und **M9**) überlegen. *Hartwig et al.* berichteten, dass Aminierungsreaktionen von *N*-Heteroarylchloriden oder Arylchloriden mit Palladiumkomplexen des sterisch anspruchsvollen Josiphos-Typ-Liganden **B11** bereits mit Katalysatorbeladungen ab 0.005 mol% quantitativ erfolgen können.[227-229] Ein kürzlich erschienener Übersichtsartikel von *Fihri, Hierso et al.* fasst Synthese, Eigenschaften und katalytische Anwendung der wichtigsten Ferrocenyldiphosphine zusammen.[230]

Xantphos

Eine gute Kombination aus leichter, preiswerter Synthese und hoher chemischer Variabilität weist der von *van Leeuwen et al.* entwickelte Diphosphinligand Xantphos[231, 232] (**B12**) auf. Die *ortho*-dirigierende Wirkung des Xanthen-Heteroatoms ermöglicht die selektive Lithiierung des Xanthengrundkörpers mit *s*BuLi/TMEDA. Die entsprechenden Xantphos-Derivate sind durch anschließende *in situ* Reaktion mit Diphenylphosphinchlorid zugänglich (Abb. 32).[233]

Abbildung 32. Synthese der Diphosphine des Xantphos-Typs.

Xantphos wurde zunächst hauptsächlich in rhodiumkatalysierten Hydroformylierungsreaktionen[234] eingesetzt. Aufgrund seines Xanthen-Rückgrats verfügt Xantphos über einen extrem großen und starren Bisswinkel und ist deshalb leicht in der Lage, katalytisch aktive, *trans*-ständige Pd-Komplexe zu bilden.[235] Die gute Komplexstabilität verhilft Xantphos zu hervorragenden katalytischen Eigenschaften und hohen Selektivitäten bei *α*-Arylierungsreaktionen von Nitrilen[236] oder insbesondere Buchwald-Hartwig-Aminierungen mit Brom-[237-240] und Chlor-Heteroaromaten,[232, 241-244] bei denen hochaktive Monophosphine oft versagen. Eine interessante Anwendung von Pd-Xantphos-Komplexen ist die Synthese sonst umständlich zu synthetisierender, substituierter 1,2,3-Triazole. *Barluenga et al.* fanden kürzlich durch Pd-Xantphos katalysierte Umsetzung der entsprechenden Alkenylbromide mit Natriumazid einen bequemen Zugang zu dieser attraktiven Substanzklasse (Abb. 33).[245] Interessanterweise erwiesen sich Pd-Komplexe mit anderen Liganden, beispielsweise hochaktiven Monophosphinliganden des Biaryltyps, oder auch mit dem zweizähnigen BINAP unter identischen Bedingungen als völlig inaktive Katalysatorsysteme für diesen Reaktionstyp.

Ligand	Umsatz [%]
PPh_3	15
DavePhos (**M5**)	0
JohnPhos (**M7**)	0
XPhos (**M8**)	0
BINAP (**B7**)	0
Xantphos (**B12**)	100
-	0

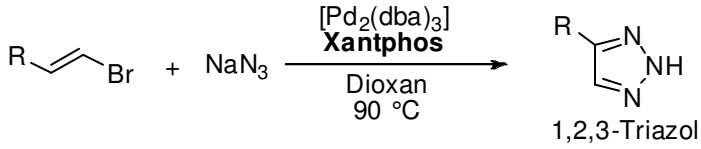
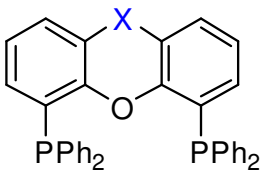


Abbildung 33. Pd-Xantphos vermittelte Triazolsynthese.



Ligand	X	natürlicher Bisswinkel β_n [°]
Homoxantphos	CH_2-CH_2	102.0
Phosxantphos	PPh_2	107.9
Sixantphos	$Si(CH_3)_2$	108.5
Thixantphos	S	109.6
Xantphos	$C(CH_3)_2$	111.4
Isopropxantphos	$C{=}C(CH_3)_2$	113.2
Benzylnixantphos	NBn	114.1
Nixantphos	NH	114.2

Abbildung 34. Variation des Bisswinkels in Abhängigkeit von der Modifikation des Xantphos-Rückgrats.

Dank seiner guten Variabilität lässt sich beispielsweise durch kleine Modifikationen am Rückgrat leicht der Bisswinkel variieren (Abb. 34).[246]

Durch Sulfonierung von Xantphos erhält man einen doppelt sulfonierten Diphosphinliganden, dessen Pd-Komplexe eine exzellente Wasserlöslichkeit aufweisen und sich in Katalysereaktionen in wässrigen Reaktionsmedien einsetzen lassen.[247]

1.2.3. Mehrzähnige Phosphine

Der Ferrocenkörper stellt ein optimales Rückgrat für eine Vielzahl mehrzähniger Phosphine dar. Ein kürzlich erschienener Übersichtsartikel von *Hierso*, *Smaliy*, *Amardeil* und *Meunier* beschreibt ausführlich Synthese und katalytische Anwendung einer großen Zahl mehrzähniger Ferrocenylpolyphosphine.[248] Die gute katalytische Aktivität der Ferrocenylpolyphosphine schreiben die Autoren der außerordentlichen Langlebigkeit der Palladiumkomplexe aufgrund der chelatisierenden Eigenschaften (Komplexstabilität) zu. Für Pd-Komplexe der beiden in Abbildung 35 gezeigten Ferrocenylpolyphosphine **C1** und **C2** wurden sehr hohe Turnoverzahlen in Suzuki- und Sonogashira-Kreuzkupplungsreaktionen festgestellt.[249, 250] Dies bestätigt die These der Katalysatorlanglebigkeit.

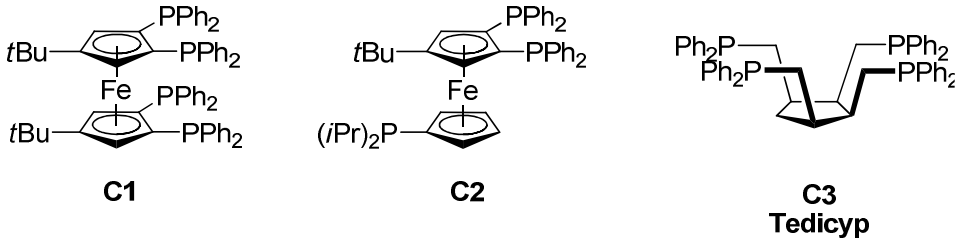


Abbildung 35. Übersicht einiger Polyphosphinliganden.

Tedicyp

Einer der bekanntesten und aktivsten Polyphosphinliganden in diesem Zusammenhang ist der von *Doucet*, *Santelli et al.* entwickelte vierzähnige Ligand Tedicyp (**C3**).[251, 252]

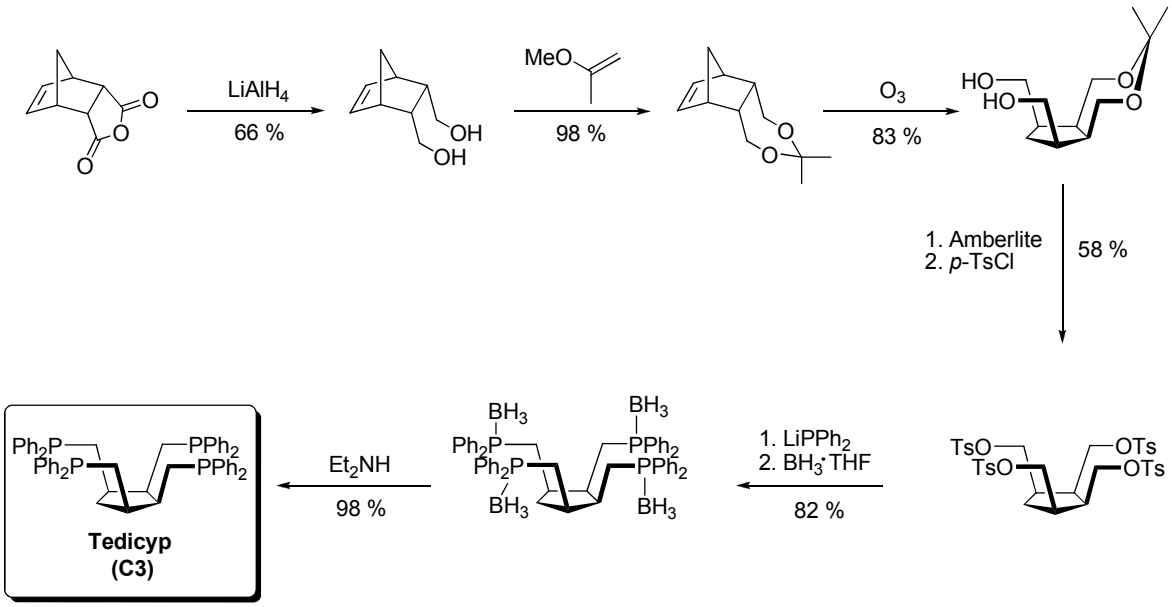


*Abbildung 36. Synthese von Tedicyp (**C3**).*

Die Synthese des Tetraphosphinliganden Tedicyp verläuft wie in Abbildung 36 gezeigt über sechs Schritte: Reduktion von Norbonendicarbonsäureanhydrid zum Diol, Umsetzung mit 2-Methoxypropen, Ozonolyse und anschließende Tosylierung ergeben als wichtiges Intermediat das abgebildete Tetratosylat. Die Darstellung des Tetraphosphins erfolgt durch Umsetzung des Tetratosylats mit Lithiumdiphenylphosphid. Als Boranaddukt ist das Tetraphosphin luft- und lagerstabil, die Entschützung zum freien Phosphin erfolgt in der Regel erst kurz vor dem Einsatz als Ligand in den entsprechenden Kreuzkupplungen.[251] Die Gesamtausbeute beträgt rund 25 % über alle sechs Reaktionsschritte. Einige Optimierungsarbeit wird folglich nötig sein, um Tedicyp wirtschaftlich als Ligand in Kreuzkupplungsreaktionen im technischen Maßstab einzusetzen.

Die hohe katalytische Aktivität von Palladiumkomplexen mit Tedicyp wird verschiedenen, diesen Liganden auszeichnenden Eigenschaften zugeschrieben. Es wird vermutet, dass die vier auf derselben Seite eines Cyclopentylrings fixierten Diphenylphosphinogruppen eine koordinative Stabilisierung bewirken. Dadurch ist der Pd-Komplex unempfindlicher gegenüber erhöhten Temperaturen und koordinierenden („vergiftenden“) Substraten als klassische Pd-Komplexe mit Monophosphinen wie beispielsweise $[Pd(PPh_3)_4]$. *Doucet* und *Santelli* konnten aufgrund von NMR-Untersuchungen zeigen, dass das Pd^0-Zentrum aufgrund des hohen „Zwangs zur Koordination“ regelrecht zwischen den vier Phosphinliganden zirkuliert.[253] Darüber hinaus verfügt der Pd/Tedicyp-Komplex über gute sterische und elektronische Eigenschaften. Pd/Tedicyp zeigte sowohl in Heck-,[254-256] Suzuki-[257, 258] oder Sonogashira-Kupplungsreaktionen[259-261] als auch in direkten Pd-

katalysierten Arylierungen von Furanen[262] oder Thiophenen[263] bemerkenswerte katalytische Aktivitäten mit heterocyclischen und nichtheterocyclischen Halogenaromaten.

1.3. Vorteile mehrzähniger Liganden bei der Kupplung heterocyclischer Substrate

Bei genauerer Betrachtung der bisherigen Übersicht über die Entwicklung von Phosphinliganden ist festzustellen, dass der Einsatz mehrzähniger Liganden bei Kreuzkupplungen heterocyclischer Substrate oder freier Amine vorteilhaft sein kann. Mit Monodentaten gebildete Palladiumkomplexe stoßen hier bisweilen an ihre Grenzen, was im Folgenden genauer analysiert werden soll.

Heterocyclen stellen Strukturelemente in vielen Naturstoffen dar und sind deshalb von besonderem Interesse für die pharmazeutische Chemie und Feinchemie.[4, 8, 264-268] Daher spielen sie als Substrate in Kreuzkupplungsreaktionen eine wichtige Rolle. Viele heterocyclische Verbindungen sind jedoch nicht ohne Weiteres in Kreuzkupplungsreaktionen einsetzbar, da sie an das Pd-Zentrum koordinieren können und somit den eigentlichen Katalysator „vergiften“, d.h. deaktivieren.[257, 269] Pyridine stellen ein Beispiel für solche heterocyclischen Katalysatorgifte dar; aber auch Ammoniak oder primäre Amine, beispielsweise Benzylamin, sind bekannt für ihre deaktivierende Wirkung auf Pd-Katalysatoren.[270, 271] Im Folgenden soll die Katalysatordeaktivierung durch Amine und Pyridine näher betrachtet werden.

Zunächst stellt sich die Frage, in welchem Schritt des Katalysecyclus‘ die Deaktivierung durch *N*-Donoren erfolgt.

a) Deaktivierung auf der Stufe der Pd^{II}-Spezies

Nach dem ersten mechanistischen Schritt, der oxidativen Addition, liegen Pd^{II}-Spezies vor. Für Pd^{II}-Komplexe konnten *Hartwig,*[227, 229] *Buchwald*[271] und *Jutand*[272] in unabhängigen Untersuchungen die Substitution sowohl von Triarylphosphinen wie $P(o\text{Tol})_3$ oder PPh_3 als auch von hochaktiven Trialkylphosphinliganden wie $Pt\text{Bu}_3$ durch Amine und Pyridine nachweisen (Abb. 37). Hierbei ist zu unterscheiden, ob das Palladiumzentrum mit sterisch anspruchsvollen oder sterisch weniger anspruchsvollen Phosphinliganden komplexiert ist. Für sterisch anspruchsvollere Liganden konnten *Buchwald* und *Hartwig* zeigen, dass *N*-Donoren den Phosphinliganden der $Pd^{II}L_1$-Spezies substituieren können. Mit einem Überschuss an *N*-Donor bilden sich Palladiumdiaminkomplexe aus, die in

Buchwald-Hartwig-Aminierungsreaktionen über keine katalytische Aktivität mehr verfügen.[227, 229, 271] Insbesondere im Fall von Pd/P*t*Bu$_3$-Komplexen erscheint die Substitution der stärker basischen, sterisch anspruchsvollen Phosphinliganden durch die weniger basischen *N*-Donoren zunächst überraschend. Der Grund mag in der stärkeren Neigung des relativ harten Pd^{II}-Zentrums zur Koordination mit dem harten Stickstoffdonor anstelle des weicheren Phosphordonors liegen.

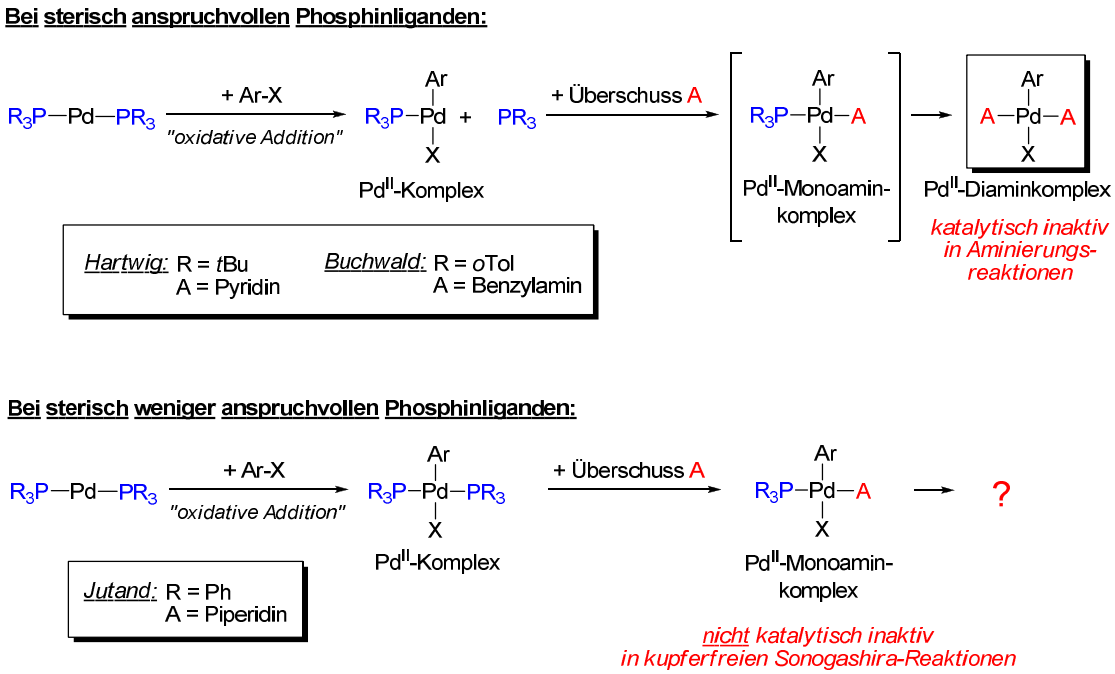


Abb. 37. Substitution von Phosphinliganden am Pd^{II}-Komplex durch N-Donoren.

Jutand untersuchte den Einfluss von Aminen auf Palladiumkomplexe mit Triphenylphosphin-Liganden, welche einen geringeren sterischen Anspruch aufweisen. Anstelle von Pd^{II}L$_1$-Komplexen liegen hier aufgrund des veränderten sterischen Anspruchs Pd^{II}L$_2$-Komplexe als katalytisch aktive Spezies im Katalysecyclus vor. Auch in diesen Komplexen konnte *Jutand* die Substitution eines Phosphinliganden durch Piperidin als *N*-Donor beobachten (Abb. 37).[272] In kupferfreien Sonogashira-Reaktionen[273] zeigte sich der resultierende Pd^{II}-Monoaminkomplex jedoch nicht katalytisch inaktiv, da die konkurrierenden Acetylene bessere Liganden darstellen und die Aminliganden aus dem Komplex zu verdrängen vermögen. *Jutand* berichtete im Gegensatz zu *Buchwald* und *Hartwig* nicht von der Bildung von Pd^{II}-Diaminkomplexen unter den gewählten Reaktionsbedingungen kupferfreier Sonogashira-Reaktionen.

b) Deaktivierung auf der Stufe der Pd^0-Spezies

Ein uneinheitliches Bild bietet sich ebenfalls bei der Betrachtung der Phosphinliganden-substitution auf der Stufe der Pd^0-Spezies: Für $[Pd(PtBu_3)_2]$-Komplexe konnte *Hartwig* keine Ligandensubstitutionsreaktion mit Benzylamin oder Pyridin als *N*-Donoren feststellen (Abb. 38).[227]

Für $[Pd(PPh_3)_2]$-Komplexe postuliert *Jutand* hingegen die Substitution eines Phosphinliganden durch Piperidin oder Morpholin.[272] Die sich bildenden Pd^0-Monoaminkomplexe sind - laut *Jutand* - reaktiver bezüglich oxidativer Additionsreaktionen als die Pd^0-Diphosphinkomplexe.

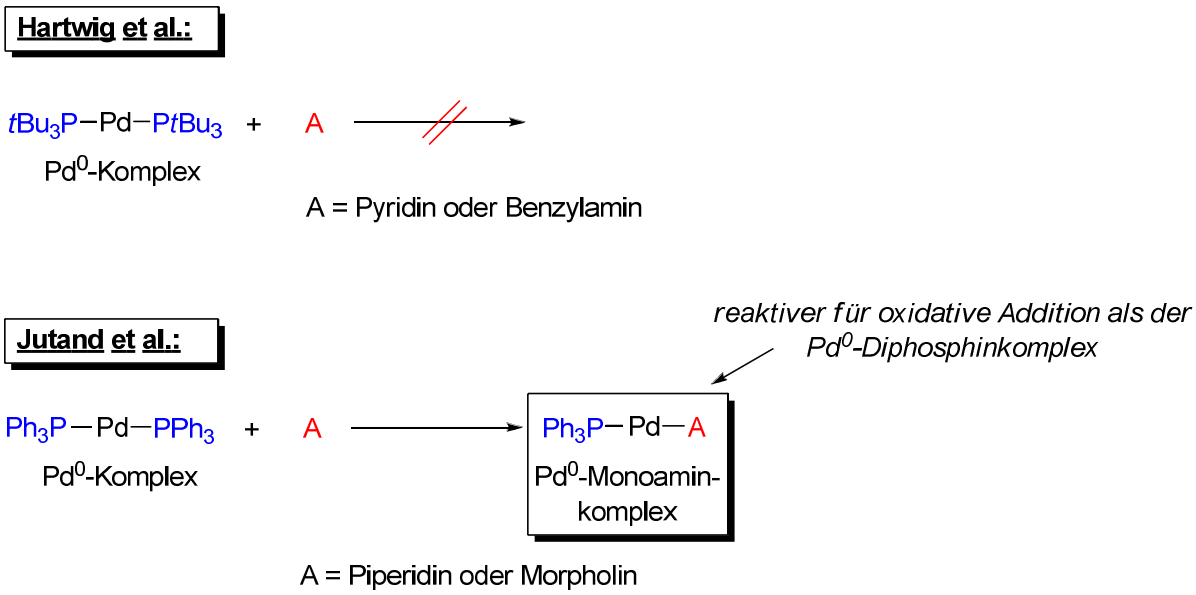


Abb. 38. Substitution von Phosphinliganden am Pd^0-Komplex durch N-Donoren.

Wie zu erkennen ist, können allgemeingültige Antworten auf die Frage nach den genauen Ursachen der Katalysatordeaktivierung durch *N*-Donoren folglich noch nicht zufriedenstellend gegeben werden. Derartige Deaktivierungen scheinen von vielen Einflussgrößen abhängig zu sein, beispielsweise den sterischen Eigenschaften der Phosphinliganden und des *N*-Donors, den σ-Donoreigenschaften und der π-Acidität der konkurrierenden Liganden sowie einer Vielzahl anderer Reaktionseinflüsse. Der folgende Abschnitt gilt deshalb Katalysatordeaktivierungen unter realen Katalysebedingungen. Anhand einzelner Beispiele sollen im Speziellen Deaktivierungen durch heterocyclische Substrate betrachtet sowie Lösungsmöglichkeiten dieser Problematik aufgezeigt werden.

Ein Beispiel für eine solche Katalysatordeaktivierung wurde 1996 durch *Buchwald et al.* beschrieben. Typische Aminierungsprotokolle mit $Pd^0/P(o\text{-Tol})_3$ als Katalysator versagen nach *Buchwald*, sobald Pyridin anwesend ist oder Halogenpyridine als Substrate

umzusetzen sind.[274] Als Liganden mit guten σ-Donoreigenschaften in Verbindung mit ausreichender π-Acidität komplexieren Pyridine mit dem Pd-Katalysatorkomplex unter Bildung eines katalytisch inaktiven Pd-Dipyridinkomplexes und Freisetzung des Phosphinliganden. Durch Zugabe von Pyridin zum $Pd^0/P(o\text{-Tol})_3$-Komplex nach erfolgter oxidativer Addition eines Halogenaromaten (ArX) gelang *Hartwig* der Nachweis der Bildung eines solchen Dipyridinkomplexes (Abb. 39).[270]

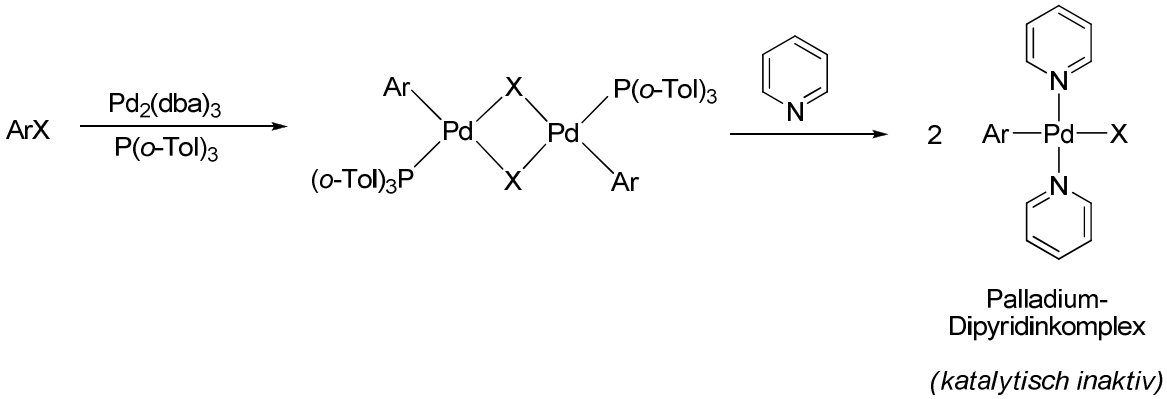


Abbildung 39. Deaktivierung des Pd-Katalysators durch Pyridine.

Mit der Verwendung chelatisierender Diphosphinliganden wie BINAP fand *Buchwald* schließlich eine gute und allgemeine Möglichkeit zur palladiumvermittelten Aminierung von Halogenpyridinen. Durch die erhöhte Komplexstabilität des mit BINAP gebildeten Palladiumkomplexes lässt sich die Bildung der inaktiven Palladiumdipyridinkomplexe verhindern.[274]

Ein weiteres Beispiel für Katalysatordeaktivierung durch Pyridinsubstrate ist die Carbonylierung von 2-Chlorpyridinen. Bei der Verwendung von Standardmonophosphinliganden wie Triphenylphosphin oder Tricyclohexylphosphin ist schnell eine Deaktivierung des Pd-Katalysators zu beobachten. Grund hierfür ist die Dimerbildung des Produkts der oxidativen Addition aufgrund der Koordination des Pyridins an das Pd-Zentrum (Abb. 40). Dieses Dimer erweist sich als katalytisch inaktiv, es reagiert nicht wie gewünscht mit Kohlenmonoxid weiter.

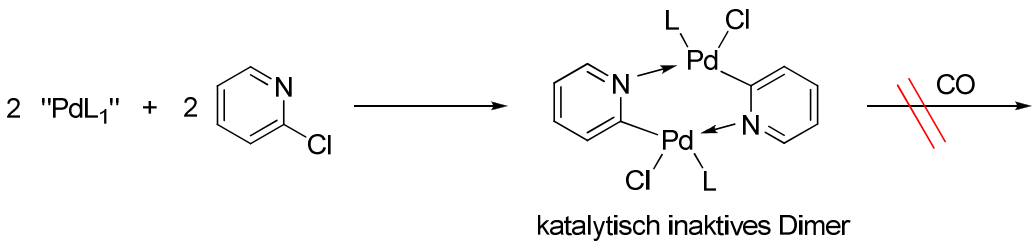


Abbildung 40. Deaktivierung durch Dimerisierung des oxidativen Additionsprodukts.

Beller et al. fanden 2001, dass sich eine solche Dimerisierung durch die Verwendung chelatisierender Phosphine wie DPPB (**B4**) oder DPPF (**B8**) verhindern lässt und entwickelten auf dieser Basis ein robustes Reaktionsprotokoll zur Carbonylierung von Chlorpyridinen.[275]

Pyridine mit ungeschützten Aminofunktionalitäten können aus zweierlei Hinsicht äußerst problematische Kupplungssubstrate darstellen:

a) erhöhte Basizität des Pyridinkörpers

Während mit Schutzgruppen (Anilid, Boc, Fmoc…) versehene Aminofunktionalitäten in der Regel die Elektronendichte und damit die Basizität des Pyridinkörpers herabsetzen, erhöhen ungeschützte Aminogruppen die Elektronendichte und die Basizität aufgrund der bekannten induktiven und mesomeren Effekte. Die Basizität korreliert direkt mit der Neigung der Pyridine zur Koordination mit dem Palladiumzentrum. Abbildung 41 zeigt die pK_a-Werte verschiedener Aminochlorpyridine, die wichtige Substrate in Kupplungsreaktionen für pharmazeutische Verbindungen darstellen. Die große Bandbreite der Basizität in Abhängigkeit vom Substitutionsmuster wird deutlich.

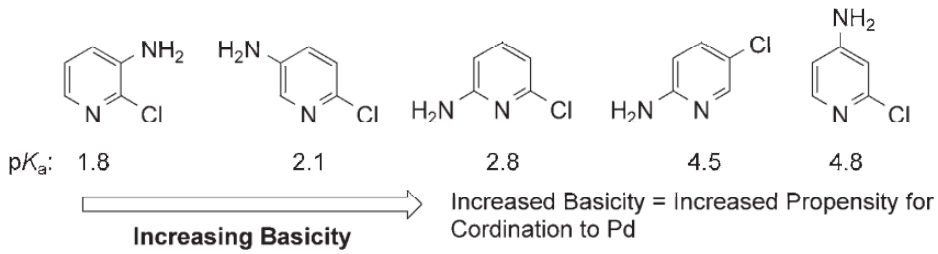
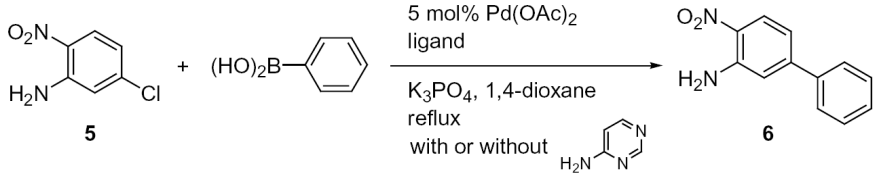


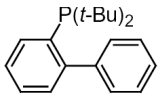
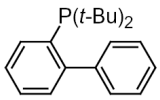
Abbildung 41. Basizität und Koordinationsneigung verschiedener Aminochlorpyridine.[276]

Dabei sinkt die Effizienz von Pd-Kreuzkupplungen mit steigender Koordinationsneigung der Aminochlorpyridine, welche beispielsweise als Substrate eingesetzt werden. *Itoh et al.* verglichen die einzelnen hier dargestellten Aminochlorpyridinderivate im Rahmen eines Suzuki-Screenings. Das am stärksten basische 4-Amino-2-chlorpyridin stellte in Suzuki-Reaktionen das anspruchsvollste Substrat dar und war unter den gewählten Bedingungen nur schwer umzusetzen (30 % Ausbeute).[222] Im Vergleich dazu reagierte das deutlich schwächer basische 3-Amino-2-chlorpyridin problemlos nach Wunsch ab (93 % Ausbeute).

b) chelatisierende Eigenschaften

Es ist bekannt, dass Pyridine oder Pyrimidine mit ungeschützten Aminofunktionalitäten in *o*-Position zum aromatischen Stickstoff Palladiumkatalysatoren durch Bildung eines Palladiumdiaminkomplexes inhibieren. Beleg hierfür sei das 2005 von *Itoh* veröffentlichte, in Abbildung 42 dargestellte Experiment.[222] 3-Chlor-4-nitroanilin lässt sich wie bei *Itoh* beschrieben mit Phenylboronsäure kuppeln. Hierbei zeigen die Pd-Komplexe der beiden eingesetzten Phosphinliganden, nämlich des zweizähnigen Bis-di*tert*butylphosphinoferrocens und des einzähnigen Buchwald-Liganden Biphenyldi*tert*butylphosphin, ähnlich hohe katalytische Aktivitäten (Einträge 1 und 2; 92 % bzw. 91 % Ausbeute). Eine signifikante Deaktivierung des mit dem als hochaktiv bekannten Buchwaldliganden gebildeten Komplexes tritt bei Anwesenheit von 50 mol% 4-Aminopyrimidin ein (Eintrag 4, 26 % Ausbeute). Der mit dem Bidentatliganden Bis-di*tert*butylphosphinoferrocen gebildete Komplex büßt hingegen in Gegenwart von 4-Aminopyrimidin keine Aktivität ein (Eintrag 3, 90 % Ausbeute).



Entry	Ligand[a]	4-Aminopyrimidine	% Yield of **6**
1	D-*t*-BPF	None	92
2		None	91
3	D-*t*-BPF	50 mol %	90
4		50 mol %	26

[a] 5 mol % of D-*t*-BPF, 10 mol % of monodentate phosphine ligand.

Abbildung 42. Vergleich der Aktivität einzähniger und zweizähniger Liganden bei Zusatz des Inhibitors 4-Aminopyrimidin.[222]

Itoh begründete die Abnahme der katalytischen Aktivität der mit Monophosphinen gebildeten Palladiumkomplexe mit Komplexierung durch das Substrat. Aminopyrimidine stellen potentielle chelatisierende Liganden dar und können an aktive Katalysatorzentren koordinieren und diese deaktivieren. Eine solche Deaktivierungsabfolge ist in Abbildung 43 (unterer Ast) gezeigt. Der auftretende Diaminkomplex besitzt keine katalytische Aktivität, der Insertionsschritt des Katalysators in die Kohlenstoff-Halogen-Bindung

(oxidative Addition) kann nicht oder nur langsam erfolgen. Hingegen weisen Pd-Komplexe mit chelatisierenden Diphosphinen als Aktivliganden eine andere Komplexstabilität auf, so dass die Bildung eines Diaminkomplexes unterdrückt wird. Die gewünschte Kupplungsreaktion kann, wie im oberen Ast in Abbildung 43 angedeutet, zügig erfolgen.

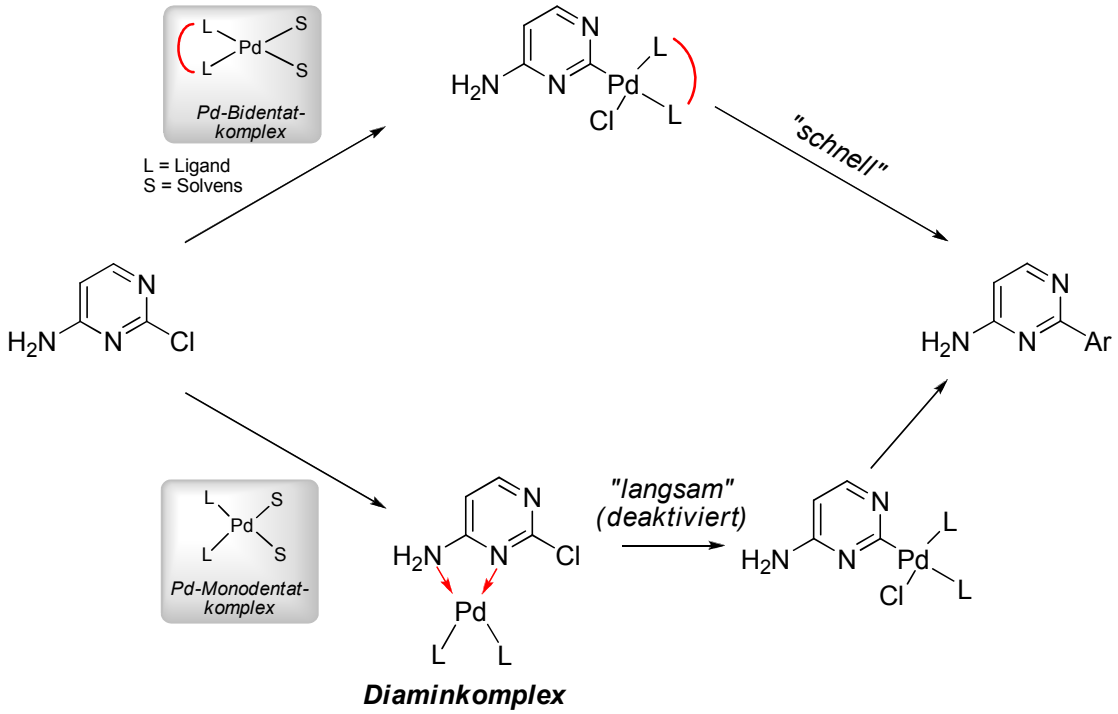


Abbildung 43. Deaktivierung des Pd-Katalysators durch chelatisierende Substrate / Vorteile bidentater Phosphinliganden.

Eine mögliche Lösung für die Problematik der Katalysatordeaktivierung stellt somit die Verwendung chelatisierender Liganden, z.B. Diphosphinliganden oder Multiphosphinliganden, dar.[230, 248, 277] Die erhöhte Komplexstabilität der resultierenden Multiphosphin-Pd-Komplexe erschwert eine substratkoordinative Katalysatordeaktivierung. Die hervorragenden Katalyseergebnisse mehrzähniger Liganden wie beispielsweise Tedicyp (**C3**) sind unter diesem Blickwinkel besser zu verstehen.

1.4. Sterik und Elektronik: Einflussgrößen auf die katalytische Aktivität

Wie bereits eingangs erwähnt, üben sterische und elektronische Parameter der beteiligten Liganden einen signifikanten Einfluss auf die Aktivität des in der Katalyse eingesetzten Übergangsmetallkomplexes aus. Der Einfluss von Phosphinen als Liganden wurde zum ersten Mal bei der Entdeckung der Klasse der Wilkinson-Hydrierkatalysatoren

$[RhCl(PAr)_3]$[278] deutlich. Man erkannte, dass unterschiedliche Substitutionsmuster am aromatischen System und damit Variation der sterischen und elektronischen Umgebung des Zentralmetalls in einer Veränderung der Aktivität des Komplexes resultieren.[279] Als Folge vielfältig angestrengter Untersuchungen unterschiedlichster Liganden - in der Hauptsache Phosphinliganden - etablierten sich zwei Parameter, mit denen sich die sterische und elektronische Natur der Liganden beschreiben lässt: Der *Tolman Kegelwinkel (cone angle)* sowie der *Tolman Electronic Parameter (TEP)*. Diese beiden Größen ermöglichen die unabhängige Betrachtung sterischer und elektronischer Eigenschaften. Dies ist mit vielen anderen gängigen analytischen Verfahren, beispielsweise der Kernresonanzspektroskopie, nur sehr begrenzt möglich; die sterisch-elektronisch unabhängige Interpretation chemischer Verschiebungen von ^{1}H, ^{13}C, ^{31}P oder Solvenssignalen ist recht komplex und zum Teil wenig verstanden.[280, 281]

1.4.1. Der Tolman Kegelwinkel

Der sterische Parameter θ (Tolman Kegelwinkel) wird bei symmetrischen Phosphinliganden (drei gleiche Substituenten) durch den Spitzwinkel eines zylindrischen Kegels beschrieben, der sich aus dem in Abbildung 44 gezeigten Modell ergibt. Die Spitze des Kegels bildet das Zentralmetall (**M**), an das der Phosphinligand in einem definierten Abstand von 228 pm koordiniert ist. Je nach sterischem Anspruch des Liganden, d.h. je nach Größe der Reste R ergibt sich nun ein Kegel, dessen Seiten von den äußeren Atomen des Liganden aufgespannt werden. Für sterisch anspruchsvolle Liganden ergibt sich dementsprechend ein größerer θ-Wert als für weniger anspruchsvolle Liganden. Tolman Winkel sterisch sehr anspruchsvoller Liganden liegen oft über 180° und werden nach Abbildung 45 ermittelt.

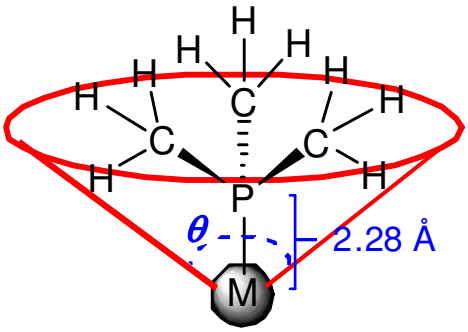


Abbildung 44. Tolman Kegelwinkel θ.

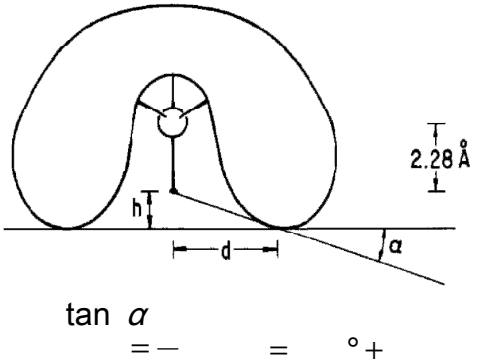


Abbildung 45. Bestimmung des Tolman-Kegelwinkel bei θ > 180°.

Kegelwinkel unsymmetrisch substituierter Liganden ($PX_1X_2X_3$) werden über die Summenbildung der jeweiligen Halbwinkel nach folgender Gleichung bestimmt:

$$\theta = \frac{3}{\sum_{i=1}^{3} \theta_i / 2}$$

Im Falle chelatisierender Diphosphine wird zur Bestimmung des Tolman Kegelwinkels dieselbe Gleichung angewandt, wobei anstelle eines der drei Substituentenhalbwinkel der halbe Bisswinkel des Diphosphins einzusetzen ist.[282] Mittlerweile wurden verschiedene Methoden zur Bestimmung des Tolman Winkels *θ* erarbeitet.[279, 283] Zur praktischen Ermittlung der Winkel werden oft Molekülmodelle bzw. Computerprogramme zu Rate gezogen. In Fällen, in denen der Tolman Winkel nur schwierig mit Hilfe geometrischer Modelle zu bestimmen ist, lässt sich die „*Degree-of-Substitution*"-Methode anwenden. Hierbei wird Nickeltetracarbonyl [$Ni(CO)_4$], unter abgeschlossenen Bedingungen mit einem definierten Überschuss an Ligand versetzt und die Menge des freigesetzten CO bestimmt. Die nach dieser Methode bestimmten Kegelwinkel stimmen erstaunlich gut mit den konventionell bestimmten Tolman Winkeln überein.[279] Auf der Basis mittlerweile unzähliger kristallographischer Daten von Phosphin-Metallkomplexen ist alternativ zu praktischen Methoden auch eine mathematisch-statistische Bestimmung des Kegelwinkels möglich.[284]

Das Kegelwinkelmodell nach *Tolman* berücksichtigt allerdings nicht, dass reale Liganden meist keine ideal zylindrische Form aufweisen. Durch Überlagerungen ist der real anfallende Kegelwinkel somit kleiner, man beobachtet höhere Koordinationszahlen.

Zudem ergeben sich Abweichungen in den realen Kegelwinkeln in Abhängigkeit von der Art des jeweiligen Zentralmetalls. Ein zeitnaher Übersichtsartikel von *Poë et al.* widmet sich konstruktiv kritisch der Thematik theoretischer und realer Tolman Kegelwinkel.[285]

1.4.2. Der Tolman Electronic Parameter (TEP)

Bereits 1967 konnten *Strohmeier et al.* zeigen, dass die Infrarot-Carbonylstreckschwingung mit den elektronischen (Donor-)Eigenschaften von (Phosphin-)Liganden korrelieren.[286] Anhand der IR-Analyse der scharfen CO-Banden einfach synthetisierbarer $Ni(CO)_3L$ Komplexe gelang *Tolman* die relative Bewertung der elektronischen Eigenschaften der Phosphinliganden.[279, 287] Der Wert der Carbonylstreckschwingung wird als Tolman Electronic Parameter ν (TEP) bezeichnet. Diese Methode erlaubt die Charakterisierung der elektronischen Eigenschaften des Liganden unabhängig von sterischen Einflussgrößen. Mit steigender e^--Donorfähigkeit der Liganden verschiebt sich ν zu kleineren Wellenzahlen. Die Bestimmung des TEP zahlreicher Phosphine erlaubt es, den einzelnen Substituenten des Phosphins TEP-Inkremente zuzuordnen. Die Addition der drei Substituenten-Inkrementfaktoren χ_i zum TEP des als Bezugsphosphins gesetzten P*t*Bu$_3$ (ν = 2056.1 cm^{-1}) ermöglicht somit eine sehr gute Abschätzung des TEP unsymmetrisch substituierter, noch nicht vermessener Phosphine:

$$\nu^{PX_1X_2X_3} = 2056.1 + \sum_{i=1}^{3} \chi_i$$

Nickeltetracarbonyl ist hoch toxisch. Deshalb werden zur Bestimmung des TEP von Liganden in letzter Zeit verstärkt die entsprechenden Iridiumkomplexe $[Ir(CO)_2Cl(L)]$ oder Rhodiumkomplexe $[Rh(CO)_2Cl(L)]$ synthetisiert.[288-290] Hierbei kann von deutlich weniger giftigen Metall-COD-Precursorkomplexen ausgegangen werden, die mit Kohlenmonoxid zu den entsprechenden Metall-Carbonylkomplexen umzusetzen sind (Abb. 46).

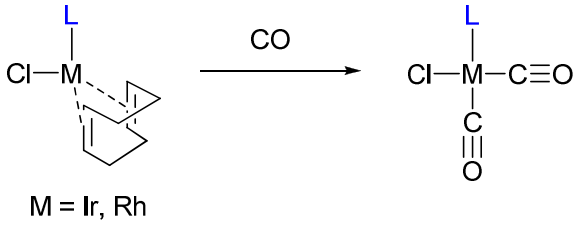


Abbildung 46. Synthese der Iridium- und Rhodium-Ligand-Carbonylkomplexe.
Die IR-Carbonylstreckschwingungen der entsprechenden Komplexe korrelieren über eine empirisch gefundene Beziehung mit den durch die Nickelkomplexe gefundenen TEPs.

Da der TEP indirekt, d.h. über den Metall-Komplex bestimmt wird, ist so keine absolute Aussage über die elektronische Donorfähigkeit des Liganden zu treffen. Eine solche isolierte Ligandencharakterisierung kann über DFT- oder MESP-Berechnungen (molecular electrostatic potential) erfolgen.[291, 292]

Eine sehr differenzierte Betrachtung der Eigenschaften für Phosphor(III)-Liganden ermöglicht das von *Giering et al.* entwickelte QALE-Modell (quantitative analysis of ligand effects).[293-296] *Giering* gelang nach Evaluierung diverser literaturbekannter physikochemischer Eigenschaften einer Vielzahl von Liganden die separierte Betrachtung von vier Eigenschaften: 1.) σ-Donorkapazität des Liganden 2.) Tolman Kegelwinkel (sterische Eigenschaften) 3.) Aryl-Effekt 4.) π-Acidität des Liganden (Abb. 47):

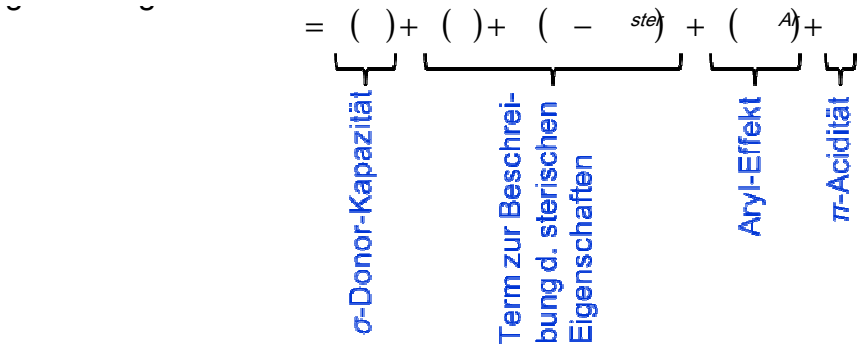


Abbildung 47. QALE-Gleichung.

Das QALE-Modell bietet außerordentlich gute Einsicht in die Natur eines Liganden. Für eine schnelle qualitative Bewertung neuer Ligandensysteme erscheint allerdings die Betrachtung des Tolman Kegelwinkels in Verbindung mit dem TEP als Mittel der Wahl.

1.4.3. Identifikation optimaler sterischer und elektronischer Ligandeneigenschaften

Wie aus dem eingangs erfolgten Überblick über Phosphinliganden erkennbar, lassen sich mit Hilfe sterisch anspruchsvoller und elektronenreicher (Phosphin-)Liganden sehr aktive Pd-Katalysatorkomplexe generieren. Zwar unterliegen die verschiedenen Arten von Kreuzkupplungsreaktionen oft unterschiedlichen Mechanismen, teilweise wechselt der Mechanismus sogar innerhalb eines Typs von Kreuzkupplungsreaktionen in Abhängigkeit von den eingesetzten Substraten und Pd-Katalysatorkomplexen.[89] Zusammenhänge zwischen Katalysatoraktivität und sterischen sowie elektronischen Eigenschaften des

Katalysators lassen sich dennoch anhand vielfältiger Beobachtungen sowie mechanistischen Untersuchungen erklären.

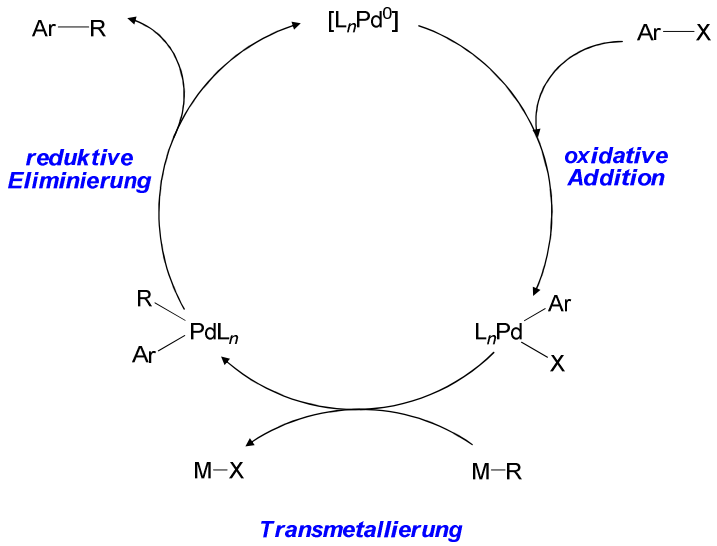


Abbildung 48. Allgemeiner Mechanismus für palladiumvermittelte Kreuzkupplungsreaktionen.[89]

Abbildung 48 zeigt einen allgemeinen Mechanismus für Pd-vermittelte Kreuzkupplungsreaktionen, aus dem sterische und elektronische Einflüsse des Phosphinliganden abgeleitet werden können:

a) Als aktive Spezies wird für sterisch anspruchsvolle Phosphinliganden oft Pd^0L_1 vermutet.[89, 297-300] Dieses wird *in situ* aus einem Pd-Precursorsalz und dem Liganden gebildet, bisweilen werden auch fertige Pd^0L_n-Komplexe eingesetzt. Sterisch anspruchsvolle Phosphine erlauben die bevorzugte Bildung des Pd^0L_1-Komplexes bzw. begünstigen die Dissoziation eines zweiten Phosphinliganden:

$$L_2Pd(X)_2 \rightleftharpoons LPd(X)_2 + L$$

Brown, Jutand et al. konnten zeigen, dass die Palladiumkomplexe mit Phosphinen geringeren sterischen Anspruchs als aktive Spezies bzw. nach der oxidativen Addition nicht als PdL_1-Spezies, sondern als PdL_2-Komplexe vorliegen.[301]

b) Elektronenreiche Phosphine können die Pd^0-Spezies besser stabilisieren und so Agglomeration und Präzipitation zu Palladiumschwarz unterdrücken.[302]

c) Elektronenreiche Phosphine erleichtern die oxidative Addition. Sie ermöglichen damit eine Beschleunigung der Katalyse sowie die Aktivierung deaktivierter Substrate, z.B. Arylchloride.[62, 89, 302, 303] Durch Erhöhung der Nucleophilie des Palladiumzentrums kann dieses leichter in die entsprechende Aryl-X-Bindung insertieren.

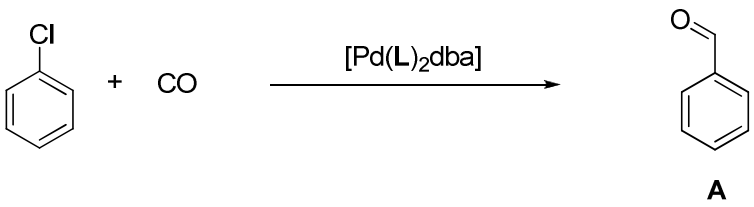
d) Sterisch anspruchsvolle Phosphine beschleunigen die reduktive Eliminierung.[43, 89, 304] Die Raumerfüllung sterisch anspruchsvoller Liganden verursacht eine Verzerrung der trigonal planaren Struktur[305] des entsprechenden Pd-Komplexes; hierdurch werden die organischen Reste räumlich enger zusammengedrängt, die reduktive Eliminierung verläuft einfacher.

Bei Buchwald-Hartwig-Reaktionen unter Einsatz von Diphosphinbidentatliganden konnte des Weiteren eine Beeinflussung der Produktselektivität in Abhängigkeit der sterischen und elektronischen Eigenschaften des Liganden festgestellt werden.[306] Der Bisswinkel beeinflusst bei Bidentatliganden als dritte „Stellgröße“ sowohl den sterischen als auch den elektronischen Charakter des Liganden.[307]

Bei der Kupplung von Arylbromiden scheint der Einfluss sterischer Aspekte der Liganden auf die Katalyseaktivität größer zu sein als der Einfluss elektronischer Eigenschaften.[107, 308] Die Aktivierung von Arylchloriden als Substrate verhält sich empfindlicher gegenüber Änderungen in den elektronischen Parametern.[308-310]

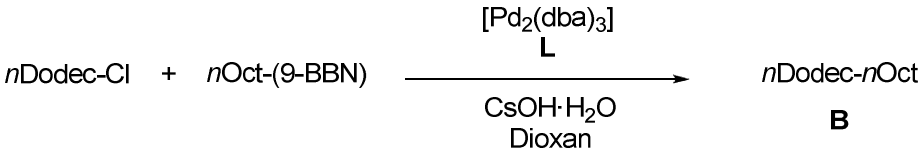
Nicht in allen Fällen jedoch korreliert die sterische Belastung der Aktivliganden mit der katalytischen Aktivität der Palladiumkomplexe in Kreuzkupplungsreaktionen. Die folgenden Beispiele sollen dies belegen. Wie aus Abbildung 49 ersichtlich, stellen Pd-Komplexe mit PCy_3 bisweilen signifikant aktivere katalytische Systeme dar als Pd-Komplexe des sterisch anspruchsvolleren P*t*Bu_3, abhängig von den gewählten Substraten. Die Palladiumkomplexe der deutlich kleineren und elektronenärmeren Phosphine P*n*Bu_3 oder PEt_3 wiederum weisen kaum katalytische Aktivität auf. Für die gezeigten Beispiele scheint folglich ein Optimum der sterischen Belastung der Phosphinliganden bei einem Tolman Winkel von $\theta \sim 170°$ vorzuliegen.

Carbonylierung:



A

Suzuki-Alkylierung:



B

	Ligand L	Cone Angle θ [°][279]	pK_a[104]	Ausbeute[104] **A**	Ausbeute[108] **B**
1	PCy_3	170	9.7	> 90 %	77 %
2	$PiPr_3$	160	8.7	> 90 %	53 %
3	$PtBu_3$	182	10.3	< 10 %	< 2 %
4	$PnBu_3$	132	8.4	n.d.	5 %
5	PEt_3	132	8.7	< 10 %	n.d.

Abbildung 49. Vergleich der Aktivität einzelner einfacher Trialkylphosphinliganden in Carbonylierung[104] und Suzuki-Reaktion.[108]

Ebenso zeigten sich in der Suzuki-Kupplung von 6-Arylsulfonylpurinen sterisch anspruchsvolle Biphenylmonophosphinliganden des Buchwald-Typs anderen Liganden desselben Typs mit geringerem sterischen Anspruch deutlich unterlegen (Abb. 50).[311]

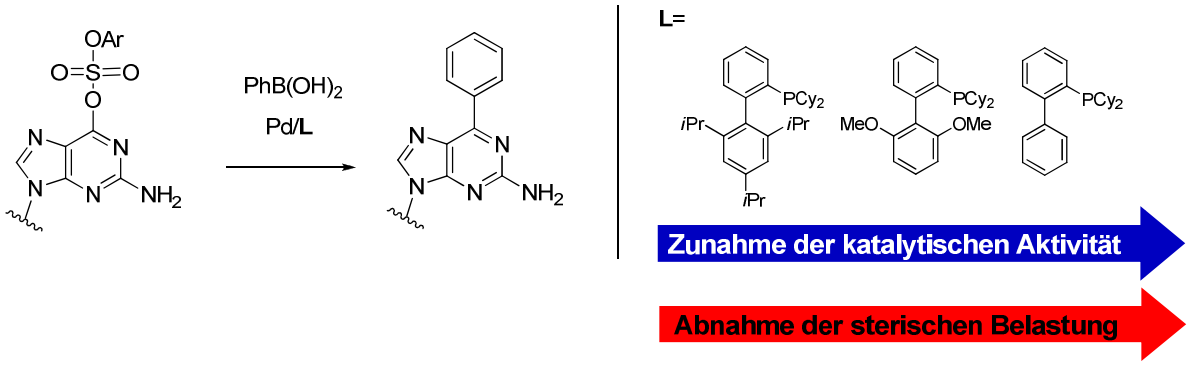


Abbildung 50. Einfluss der sterischen Belastung auf die katalytische Aktivität.

Der Vergleich verschiedener Arylbiphenylphosphine (Abb. 51) als Liganden in der Suzuki-Reaktion mit Arylchloriden zeichnet ein ähnliches Bild zugunsten des sterisch weniger anspruchsvollen P(biph)Ph_2.[312]

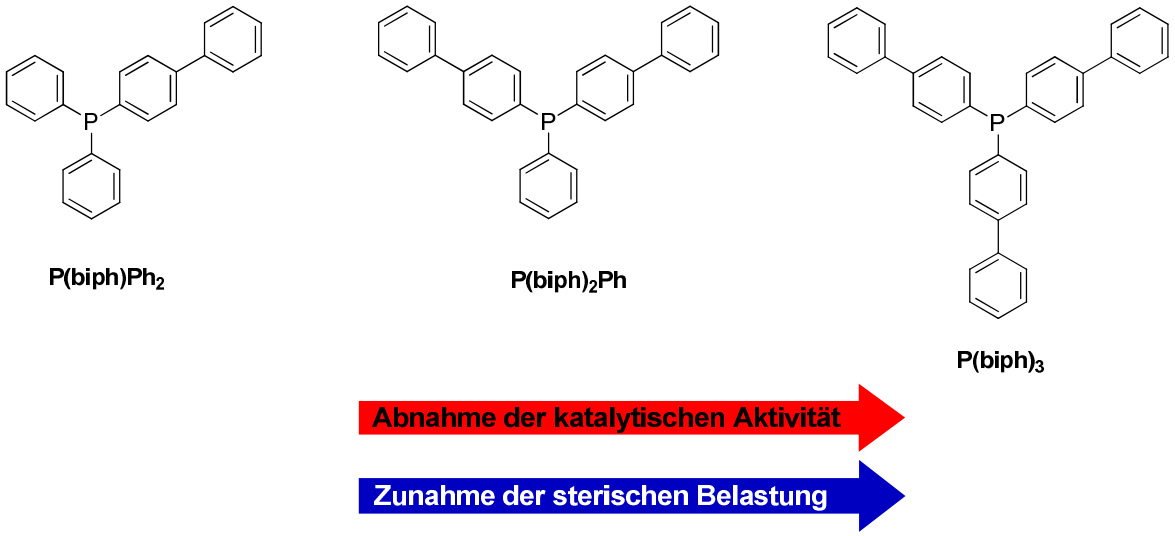


Abbildung 51. Arylbiphenylphosphine als Liganden in der Suzuki-Kupplung.

Um konkrete Zusammenhänge zwischen sterischen und elektronischen Eigenschaften von Phosphinliganden einerseits und der katalytischen Aktivität ihrer Palladiumkomplexe andererseits systematischer erfassen zu können, führten *Plenio* und *an der Heiden* kürzlich entsprechende kinetische Untersuchungen zur Sonogashira-Reaktion mit diversen Phosphinliganden durch.[107, 313] Sie konnten nachweisen, dass die hohe katalytische Aktivität von Pd-Phosphinliganden in Sonogashira-Reaktionen ein fein balanciertes Wechselspiel darstellt, nämlich zwischen den sterischen und elektronischen Eigenschaften des Aktivliganden einerseits sowie den sterischen und elektronischen Eigenschaften der Substrate andererseits.

Es ist somit unschwer zu erkennen, dass sich die katalytische Aktivität eines Pd-Phosphinkomplexes kaum vorhersagen lässt; Generalisierungen sind in der Regel nicht möglich.

1.5. Kenngrößen der katalytischen Aktivität: TON, TOF und Selektivität

Um die katalytische Aktivität verschiedener Katalysatoren miteinander vergleichen zu können, haben sich folgende Kenngrößen etabliert:

- Turnover Number (TON)
- Turnover Frequency (TOF)
- Selektivität

Auf die Bestimmung und Interpretation dieser Größen wird im Folgenden näher eingegangen.

1.5.1. Turnover Number (TON)

Die TON beschreibt die Anzahl an Substratmolekülen, die ein Katalysatorteilchen in seiner gesamten Lebenszeit bis zu seiner Inaktivierung umzusetzen vermag. Ein idealer Katalysator würde niemals inaktivieren, könnte also unendlich viele Katalysecyclen durchlaufen. Seine TON wäre unendlich groß.

$$TON = \frac{n_{\text{umgesetztes Substrat}}}{n_{\text{Katalysator}}}$$

Bei der praktischen Ermittlung ergibt sich die TON aus der Division der umgesetzten Substratstoffmenge durch die eingesetzte Katalysatorstoffmenge nach einer ausreichend großen (idealerweise unendlichen) Reaktionszeit. Die TON beschreibt somit die *Lebensdauer* oder *Stabilität* eines Katalysators.

1.5.2. Turnover Frequency (TOF)

Ein Maß für die Geschwindigkeit eines Katalysators wird durch die TOF angegeben. Sie beschreibt die umgesetzte Substratstoffmenge pro Katalysatorzentrum und Zeiteinheit, z.B. pro Stunde:

$$TOF = \frac{n_{\text{umgesetztes Substrat}}}{n_{\text{Katalysator}} * t} \left[h^{-1} \right]$$

Die praktische Bestimmung der TOF kann bisweilen einige Schwierigkeiten in sich bergen, da sich die Konzentration des Katalysators über die Zeit verändert. Deswegen stellt die TOF eine z.T. nur bedingt vergleichbare Momentaufnahme dar.

1.5.3. Selektivität

TON und TOF beziehen sich allgemein auf den Umsatz des Substrates ohne Rücksicht auf die Selektivität der Katalyse, d.h. ohne Beachtung von Nebenreaktionen. Die Selektivität beschreibt das Verhältnis zwischen Substratumsatz und selektiv gebildetem Produkt. Unter Abwesenheit von Nebenreaktionen beträgt die Selektivität 1. Die Selektivität bildet somit ein wichtiges Maß für die Güte eines Katalysatorsystems.

Isoliert betrachtet, bieten die drei Größen TON, TOF und Selektivität nur begrenzte Aussagekraft. Die Synopse der drei Faktoren ist für die Beurteilung eines Katalysators essentiell und gibt Aufschluss über die katalytische Effizienz des Systems. Ein Übersichtsartikel von *Farina*[95] zeigt die Bedeutung von TON, TOF und Selektivität für die Implementierung eines Katalysators in ein industriell chemisches Verfahren auf.

1.6. Kriterien für das Design idealer Phosphine für Pd-Kreuzkupplungen

Nach *Jones*[62] dominieren zwei Fragestellungen die Entwicklung neuer Katalysatorsysteme:

1.) Wie gelingt es, Katalysatoren zu entwickeln, die aktiv genug sind, auch Arylchloride zu aktivieren?[79, 115] Diese Substrate sind zwar in Kreuzkupplungsreaktionen schwieriger umsetzbar, jedoch oft signifikant preiswerter und besser verfügbar als andere Arylhalogenide.
2.) Wie lassen sich Katalysatorkosten sowie die Kontamination der Produkte mit dem Katalysatormetall minimieren?[95] (Gesetzliche Vorgaben erfordern meist eine jeweilige maximale Schwermetallbelastung der APIs (active pharmaceutical ingredient) von 10 ppm)[314]

Diese Kriterien sollen unter dem Stichwort „*Aktivität*“ zusammengefasst werden. Die Größen *TON*, *TOF* und *Selektivität* sind ebenfalls in diesem Bereich anzusiedeln.

Doch ist die Aktivität der einzige Faktor, der eine optimale Ligandenklasse und somit einen effizienten Katalysator ausmacht?

In der Regel werden neue Katalysatorsysteme für Pd-vermittelte Kreuzkupplungsreaktionen an „akademischen Substraten“ getestet. Dies erleichtert den Vergleich der unterschiedlichen Katalysatoren. Bei den in der pharmazeutischen Chemie zu kuppelnden Substraten handelt es sich jedoch oft um heterocyclische Substrate oder Substrate mit ungeschützten funktionellen Gruppen wie Aminen. Diese Substrate sind häufig problematisch in Kreuzkupplungsreaktionen. In typischen Screeningverfahren werden diese Substanzklassen gerne ausgeblendet.

Neben dem Katalysator hängt der Erfolg einer Kreuzkupplungsreaktion im Wesentlichen von der Wahl der Reaktionsbedingungen (Solvens, Base, Temperatur…) ab.[46] Des Weiteren erfordert das verstärkte Bestreben nach Nachhaltigkeit in Produktionsprozessen,[315-319] Kreuzkupplungsreaktionen in alkoholischen oder wässrigen Medien sowie Ionischen Flüssigkeiten zu optimieren.[320-327] Die klassischerweise für diese Reaktionen favorisierten Lösemittel wie DMF, Dioxan oder THF gilt es zu ersetzen.

Nicht jeder Ligand ist mit jedem Reaktionsprotokoll kompatibel. Aus diesem Grund ist es wünschenswert, dass ein Ligand und damit der Katalysator leicht variabel ist. Durch sterische oder elektronische Veränderungen gelingen Anpassungen des Liganden einer Klasse an unterschiedliche Substrate, andere chemische Modifikationen können die Polarität des Liganden beeinflussen und ermöglichen so die Adaption an unterschiedlichste Lösemittel.

Viele pharmazeutisch aktive Substanzen sind nicht besonders temperaturbeständig. Ein guter Katalysator sollte daher einen Substratumsatz unter milden Bedingungen ermöglichen. Dabei muss die Kupplung bei Raumtemperatur,[117, 119, 125, 135, 150, 159, 187, 328, 329] die einige Katalysatoren mittlerweile auch mit schwierigen Substraten ermöglichen, nicht unbedingt das Entwicklungsziel eines „optimalen“ Katalysators sein. Da Kreuzkupplungen exotherme Reaktionen sind, ist es bisweilen verfahrenstechnisch effizienter, Reaktionen bei noch milden, aber erhöhten Temperaturen zu fahren, z.B. zwischen 50 und 100 °C. Um dem Katalysatoranwender einen angenehmen Spielraum bezüglich der Reaktionstemperatur zu ermöglichen, ist es somit wünschenswert, wenn optimale Katalysatoraktivität sowie Katalysatorstabilität über einen breiten Temperaturbereich gegeben wären.

All diese Aspekte seien unter dem Begriff „*Variabilität*“ zusammengefasst.

Neben diesen Erwägungen, die sich in erster Linie auf die Reaktion selbst bzw. die Prozessführung beziehen, spielen für den Anwender noch weitere, nicht zu vernachlässigende Faktoren eine Rolle bei der Auswahl des Katalysators: a) die Handhabbarkeit (viele Phosphinliganden sind pyrophor, unstabil oder giftig),[330] b) Preis und Verfügbarkeit (Liganden können bisweilen teurer als das Katalysemetall sein. Für industrielle Prozesse müssen die Katalysatoren problemlos im Multi-Kilogrammmaßstab verfügbar sein).[46]

„*Sicherheit und Verfügbarkeit*“ sollen die Überbegriffe für diese Überlegungen sein.

In Abbildung 52 sind die Kriterien, die ein idealer Katalysator für Pd-vermittelte Kreuzkupplungsreaktionen aufweisen sollte, graphisch zusammengefasst. Diese Aspekte spiegeln das Ziel der gegenwärtigen Katalysatorforschung wider.

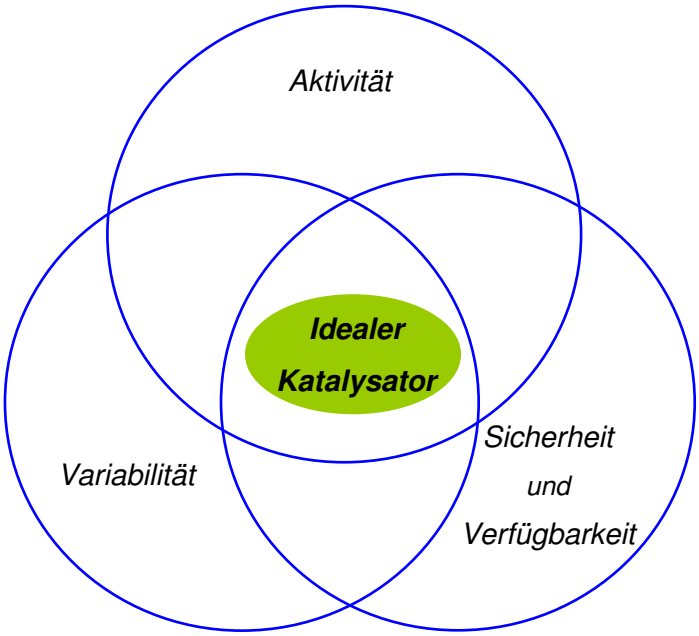
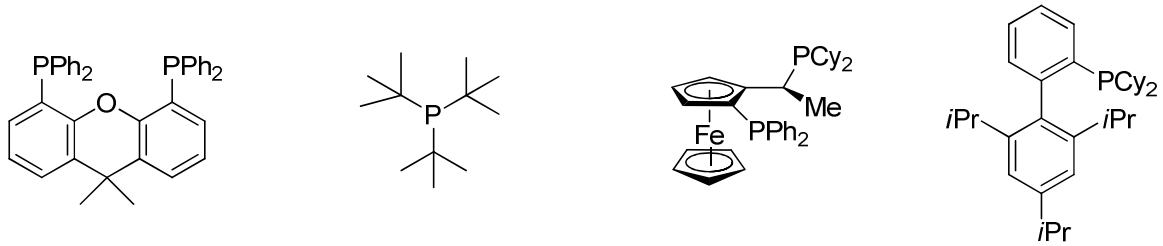


Abbildung 52. Kriterien eines idealen Katalysators für Pd-vermittelte Kreuzkupplungsreaktionen.

2. Strategische Zielsetzung der Arbeit

Vergleicht man die Eigenschaften gegenwärtig verfügbarer Liganden und Katalysatorsysteme für Kreuzkupplungsreaktionen mit den im vorangegangenen Kapitel entwickelten Idealvorstellungen, werden z.T. gravierende Defizite der aktuellen Systeme offenbar.
Bei folgenden drei häufig eingesetzten hochaktiven Phosphinliganden (Abb. 53) fallen beispielsweise folgende Defizite auf:



B12
Xantphos

M4
Tri*tert*butylphosphin

B10
Josiphos

M8
XPhos

Abbildung 53. Drei häufig in Pd-Kreuzkupplungsreaktionen eingesetzte Hochleistungsphosphine.

- Das preiswerte und oftmals selektive Xantphos (**B12**) erzielt in vielen Kreuzkupplungsreaktionen nicht die erwarteten Aktivitäten.
- Tri*tert*butylphosphin (**M4**) ist pyrophor. Eine leichte chemische Modifikation der Alkylgruppen ist in Anwesenheit des ebenfalls reaktiven Phosphorzentrums nicht gegeben.
- Josiphos (**B10**) ist ein chiraler Ligand. Dessen hohe Kosten sind in der Regel nicht durch den Einsatz in Pd-Kreuzkupplungsreaktionen zu rechtfertigen.
- XPhos (**M8**) erfüllt die aufgestellten Kriterien bereits in weiten Zügen. Herausragend ist seine hohe Aktivität in Kreuzkupplungsreaktionen. Trotz vieler Arbeiten hinsichtlich Upscaling beinhaltet die beste Variante jedoch zwei mäßig attraktive Grignard-Stufen[331] in einer „One-Pot-Synthese“. Die Gesamtausbeute der optimierten Reaktion liegt deutlich unter 60 %, somit bleibt ein substantieller Teil des teuren Edukts Dicyclohexylchlorphosphin ökonomisch ungenutzt. Darüber hinaus ist eine Derivatisierung des Liganden auf einer späten Stufe nicht zu realisieren.

Aus diesem Grund soll ein neues Ligandensystem entwickelt werden, dessen Eigenschaften dem zuvor skizzierten Ideal möglichst nahe kommen. Folgende Eigenschaften stehen hierbei für uns - im Einklang mit den geforderten Kriterien - im Vordergrund:

- hohe Katalysatoraktivität, Aktivierung von Chloraromaten
- problemlose Kupplung der für Pharma und Feinchemie wichtigen Heteroaromaten
- freie Wahl in der Verwendung der Lösemittel (freie Einstellbarkeit der Polarität des Katalysators)
- leichte Synthese des Phosphinliganden, preiswerter Zugang zu den Edukten

2.1. Entwicklung der Dialkylfluorenylphosphin-Ligandenklasse

Tri*tert*butylphosphin (**M4**) ist ein bekanntes, patentfreies Trialkylphosphin, das gerne in Pd-vermittelten Kreuzkupplungsreaktionen eingesetzt wird. Aufgrund seines sterischen Anspruchs (Tolman Winkel θ = 182°)[279] und seines elektronenreichen Charakters zeigen die entsprechenden Phosphin-Palladium-Komplexe sehr hohe Aktivitäten in einer Vielzahl von Kreuzkupplungsreaktionen. Allerdings sind die mangelhafte Variabilität, eine unvorteilhafte Synthese sowie die pyrophoren Eigenschaften inhärente Defizite von P*t*Bu$_3$. Ausgehend von Tri*tert*butylphosphin soll nun versucht werden, eine neue Ligandenklasse zu entwickeln, die unter Beibehaltung seiner Stärken die Defizite von P*t*Bu$_3$ nicht mehr aufweist.

Einen konsequenten Ansatzpunkt bei der Entwicklung einer neuen Ligandenklasse nach dem Vorbild von P*t*Bu$_3$ (**M4**) stellt das *tert*-Butyl-Motiv dar. Dessen raumerfüllender Charakter und gute σ-Donoreigenschaften sind Ursache für die gute Eignung als Ligand in Kreuzkupplungsreaktionen. Die stark begrenzte chemische Variabilität des *tert*-Butyl-Motivs ist gleichsam dessen Achillesferse: Sollen Variationen an P*t*Bu$_3$ (**4**) erfolgen, müssen diese bereits in sehr frühen Synthesestufen vorgenommen werden, eine nachträgliche chemische Modifikation des tertiären Alkylrests ist kaum möglich. Folglich ist ein chemischer Baustein zu identifizieren, in dem das *tert*-Butyl-Motiv vorhanden ist, das anstelle dieses Alkylrests als Substituent im Phosphin integriert werden kann. Durch diesen Baustein sollen die genannten Vorteile der *tert*-Butyl-Gruppe beibehalten, die chemische Variabilität jedoch gesteigert werden. Als Anforderungen an das gesuchte Synthon sind folgende Punkte zu nennen:

- Vorhandensein des *tert*-Butyl-Motivs an einer direkt zugänglichen Stelle zur leichten Anbindung an das Phosphorzentrum
- leichte chemische Variabilität, möglichst orthogonaler chemischer Zugang an verschiedenen Positionen des Bausteins
- hohe Stabilität (z.B. thermisch, chemisch), geringe Toxizität des Bausteins
- möglichst einfache Architektur des Bausteins
- preiswerter Zugang

Als Baustein, der den wesentlichen der genannten Anforderungen entspricht, lässt sich das Fluorenmotiv identifizieren. Abbildung 54 beschreibt nochmals anschaulich die „formale Verwandtschaft“ der *tert*-Butyl-Gruppe (rot) mit dem Fluorenylsystem: Abstraktion zweier *tert*-Butyl-Gruppen aus P*t*Bu$_3$ (**M4**) führt zur allgemeinen Darstellung des neuen gesuchten Ligandentyps **4x**. Substitution der *tert*-Butyl-Gruppe durch das Fluorenyl-Synthon führt zur neuen Ligandenklasse: den Dialkylfluorenylphosphinen (**4y**).

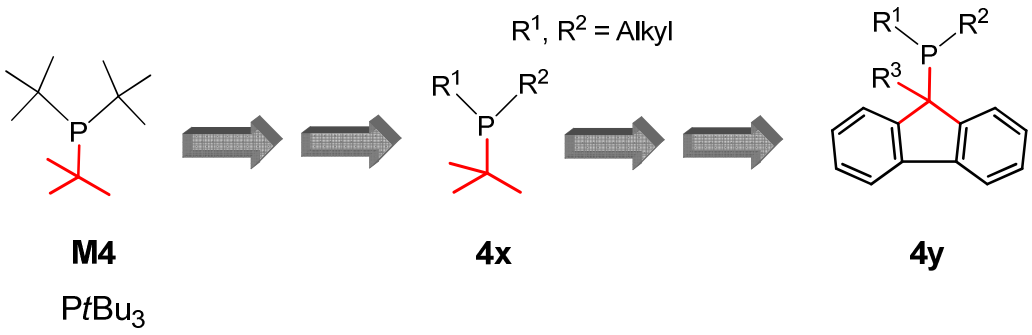


Abbildung 54. Entwicklung der Phosphinligandenklasse der Dialkylfluorenylphosphine.

Als „Träger“ des *tert*-Butyl-Motivs sollte das Fluorengerüst über ähnliche sterische und elektronische Eigenschaften wie der Alkylrest selbst verfügen. Neuartig erscheinen jedoch die mannigfaltigen chemischen Variationsmöglichkeiten, die in Abbildung 55 angedeutet werden. Die beiden CH-aciden Protonen in Position 9 des Fluorens erlauben leichte Manipulationen durch Substitutionsreaktionen und Einführung des Phosphinrests. Das aromatische Gerüst eröffnet Möglichkeiten für die volle Bandbreite aromatischer Reaktionen, vor allem aromatischer Substitutionsreaktionen.

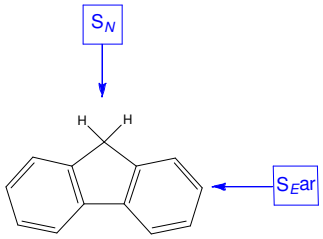


Abbildung 55. Synthetische Variationsmöglichkeiten am Fluorengerüst.

2.2. Variabilität der Dialkylfluorenylphosphine

Abbildung 56 gibt einen Überblick über die einzelnen Möglichkeiten, Variationen an den Liganden vorzunehmen:

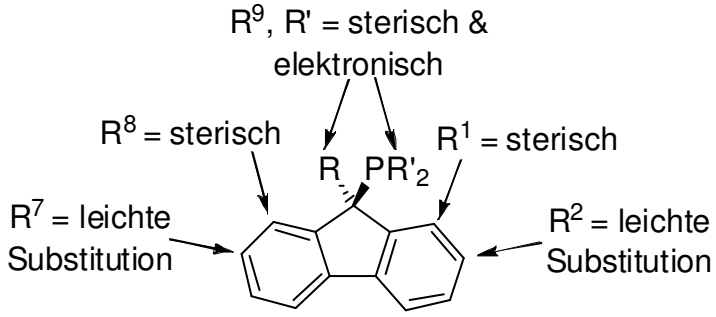


Abbildung 56. Demonstration der hohen Variabilität der Fluorenyldialkylphosphine.

- Die Reste **R'** sind variabel. Durch Auswahl unterschiedlicher (Alkyl-)Substituenten direkt am Phosphor sind sterische und elektronische Eigenschaften einstellbar.
- Aufgrund der CH-Acidität lassen sich unterschiedlichste Reste **R** selektiv an die 9-Fluorenyl-Position anbringen. Sterische Belastung und elektronische Eigenschaften des Phosphins sind somit über diese Position beeinflussbar.
- Über die Reste $\mathbf{R^1}$ und $\mathbf{R^8}$ lässt sich der sterische Anspruch des Phosphins weiter erhöhen. Die Positionen 1 und 8 sind in der Regel nicht selektiv durch einfache Substitution am Standard-Fluorengerüst zugänglich. Die selektive Besetzung dieser Positionen ist mit Hilfe einer De-Novo-Synthese des Fluorengrundkörpers zu erreichen.
- Die Positionen 2 und 7 am Fluorengerüst sind einfach und selektiv über aromatische S_E-Reaktionen zugänglich. Folglich eignen sich die Reste $\mathbf{R^2}$ und $\mathbf{R^7}$ hervorragend für verschiedenste Variationen am Phosphin, beispielsweise der Implementierung polarer oder unpolarer funktioneller Gruppen zur Adaption der Löslichkeit an verschiedene Reaktionsmedien. Auch eine Fixierung des späteren Katalysators an einem festen Träger (Heterogenisierung) sollte über diese Positionen zu erreichen sein.

Zusätzlich zu diesen aufgeführten Variationsmöglichkeiten am Phosphorzentrum und Fluorengerüst fällt auch die Variabilität des Fluorengerüsts als solches auf. Wie aus Abbildung 57 ersichtlich, liegt durch Abstraktion eines aromatischen Rings ein Indenylsystem vor. Nimmt man die Abstraktion beider aromatischer Ringe vor, wird ein Cyclo-

pentadienylsystem erhalten. Folglich lassen sich in Analogie zu den Fluorenylphosphinen auch Dialkylindenyl- sowie Dialkylcyclopentadienylphosphine synthetisieren, die - flankiert von den entsprechenden Methylsubstituenten - in ihren sterischen und elektronischen Grundzügen mit den Fluorenylphosphinen verwandt sind und entsprechende Variabilität aufweisen.

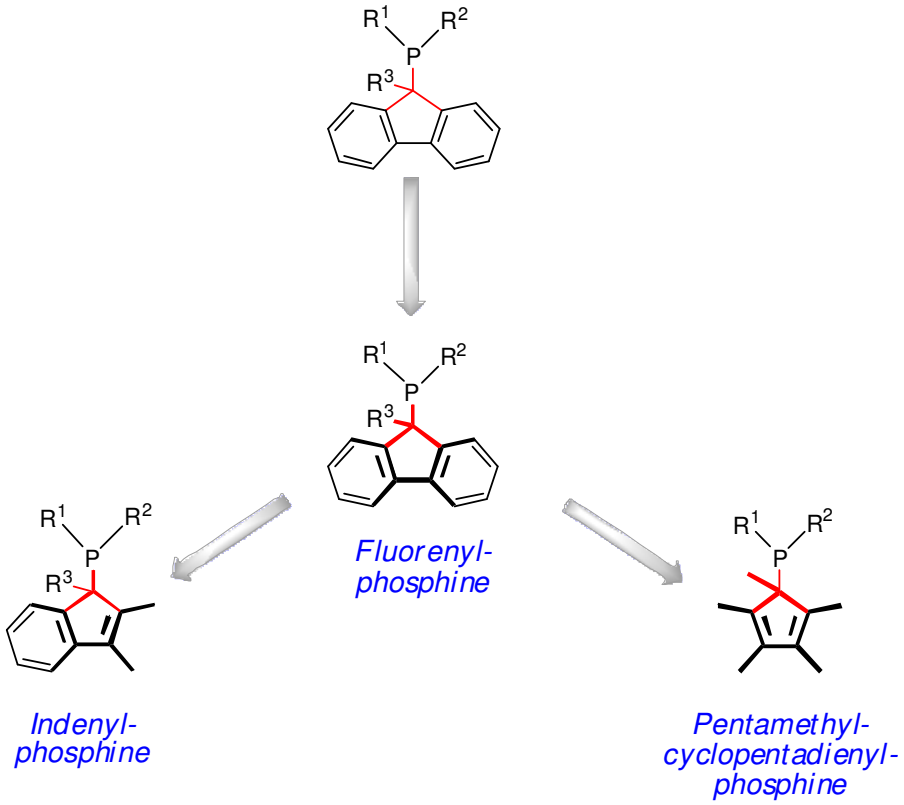


Abbildung 57. Variabilität im Grundgerüst: Verwandtschaft der Fluorenyl-, Indenyl-, und Pentamethylcyclopentadienylphosphine.

2.3. Synthesestrategie der Dialkylfluorenylphosphine

Ausgehend von preiswertem und kommerziell verfügbarem Fluoren sollte die Dialkylfluorenylligandenklasse nach der in Abbildung 58 skizzierten Route synthetisierbar sein. Nach Deprotonierung des Fluorens mit *n*-Butyllithium als Base kann das resonanzstabilisierte Fluorenylanion mit dem entsprechenden Dialkylphosphinchlorid umgesetzt werden, um das Fluorenyldialkylphosphin zu erhalten. Soll Position 9 am Fluorenyldialkylphosphin weiter substituiert sein, erscheint die Umsetzung der bekannten 9-R-Fluorenylanionen mit Dialkylphosphinchlorid sinnvoll. Eine Umkehrung der Synthesesequenz für den Fall R =

Alkyl (zunächst Einführung des Phosphorsubstituents, dann 9-Alkylierung des Fluorens) führt mit hoher Wahrscheinlichkeit nicht zum gewünschten Phosphin als Produkt. Abbildung 59 zeigt die Bildung des stabilen tertiären Phosphoniumsalzes über eine Phosphor-Ylid-Zwischenstufe. Die erhaltenen Phosphine sollen durch Reaktion mit Tetrafluoroborsäure (HBF_4) als Phosphoniumsalze gefällt werden. Die Phosphoniumsalzbildung kombiniert die Isolation der Produkte in hoher Reinheit mit guter Oxidations- und Lagerstabilität. Gewinnung und Einsatz von Phosphinen in Kreuzkupplungsreaktionen als Phosphoniumsalze wurden von unserer Arbeitsgruppe mehrfach beschrieben.[180, 332, 333]

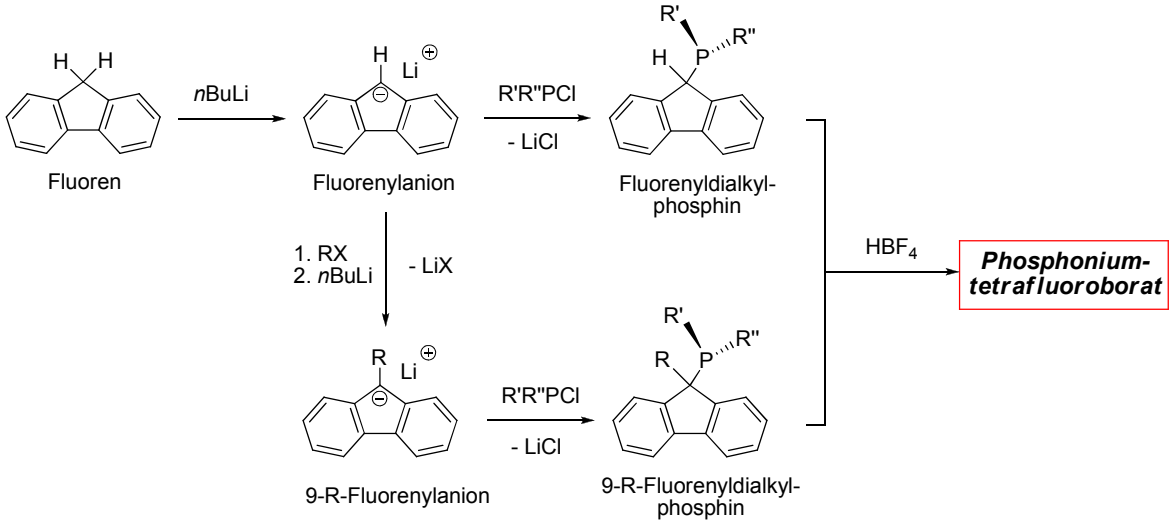


Abbildung 58. Synthesestrategie der Dialkylfluorenylphosphine.

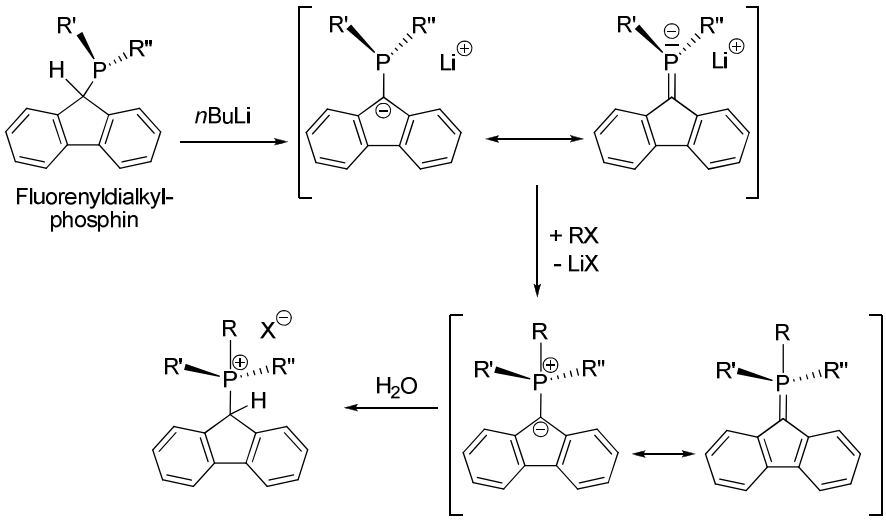


Abbildung 59. Bildung eines tertiären Phosphoniumsalzes durch Änderung der Synthesesequenz.

In der vorliegenden Arbeit sollen Synthese und Einsatzmöglichkeiten von Liganden der Fluorenyldialkylphosphinklasse explorativ erforscht werden. Besonderes Augenmerk wird hierbei auf Anwendungen in Kreuzkupplungsreaktionen heterocyclischer Substrate sowie die Etablierung nachhaltiger Verfahren in Kreuzkupplungen gerichtet.

3. Aufgabenstellung

In Kapitel 2 wurde die Motivation zur Entwicklung der neuen Phosphinligandenklasse der Dialkylfluorenylphosphine ausgehend von dem als aktiven Liganden bekannten P*t*Bu$_3$ dargelegt. Hieraus ergeben sich als Aufgabenstellung für die vorliegende Arbeit folgende drei Ziele:

1.) **Synthese** einer größeren Anzahl verschiedener Phosphine der neuen Ligandenklasse. Die Auswahl der synthetisierten Phosphine sei durch folgende Kriterien beeinflusst:

- Synthese der Phosphine auf Basis der drei identifizierten Grundkörper (Fluorenyl-, Indenyl-, Pentamethylcyclopentadienylphosphine)

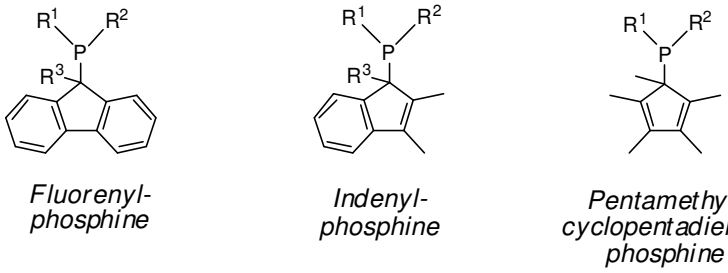


Abbildung 60. Fluorenyl-, Indenyl- und Pentamethylcyclopentadienylphosphine.

- möglichst große Bandbreite der sterischen und elektronischen Eigenschaften der Liganden

2.) **Evaluierung der Aktivität** der Palladiumkomplexe der synthetisierten Phosphine in Kreuzkupplungsreaktionen:

- Suzuki-Miyaura-Kupplung
- Sonogashira-Kupplung
- Buchwald-Hartwig-Aminierung

Ziel hierbei ist die Identifikation besonders aktiver Phosphine. Hauptaugenmerk soll auf der Umsetzung der industriell interessanten Chlor- und Bromaromaten liegen. Die Vergleichbarkeit der Aktivität der besten Dialkylfluorenylphosphine mit

bekannten leistungsstarken Phosphinen wäre eine Bestätigung für die Richtigkeit des Entwicklungskonzepts.

3.) **Anbringen einer polaren Phasenmarkierung** an ein leistungsfähiges Phosphin der neuen Ligandenklasse (Abb. 61).

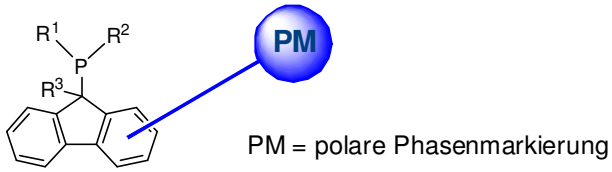


Abbildung 61. Polare Phasenmarkierung der Dialkylfluorenylphosphine.

Der phasenmarkierte Pd-Phosphinkomplex ist anschließend als Katalysator in wässrigen Kreuzkupplungen einzusetzen. Die Verwendung von Wasser als (Co)solvens soll in diesem Zusammenhang untersucht werden hinsichtlich:

a) Beeinflussung der Katalyseaktivität durch Wasser
b) Entwicklung nachhaltiger Verfahren

4. Kumulativer Teil der Dissertation

4.1. Synthese von 9-Fluorenylphosphinen und Untersuchung der katalytischen Aktivität in Kreuzkupplungsreaktionen

Der Inhalt dieses Kapitels wurde bereits veröffentlicht:

Christoph A. Fleckenstein, Herbert Plenio, *"9-Fluorenyldialkylphosphines for the Pd-Catalyzed Sonogashira, Suzuki and Buchwald-Hartwig Coupling in Organic Solvents and in Water"*, *Chem. Eur. J.* **2007**, *13*, 9, 2701-2716.

In diesem Kapitel wird die Synthese und die Evaluierung neuartiger Fluorenyldialkylphosphine in Pd-katalysierten Kupplungsreaktionen beschrieben. Bis auf wenige Ausnahmen erfolgte die Synthese analog Abbildung 62:

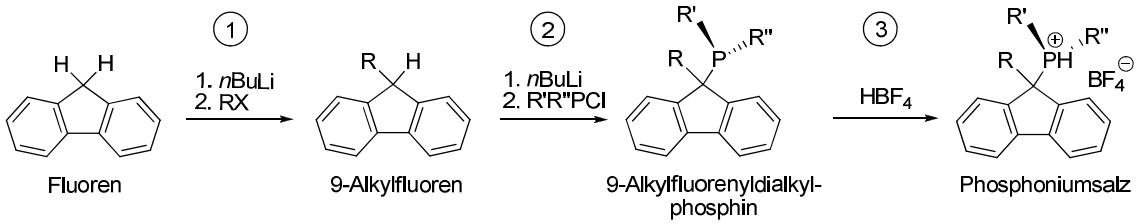


Abbildung 62. Allgemeines Syntheseschema der Fluorenyldialkylphosphine.

1.) Synthese des entsprechenden 9-substituierten Alkylfluorens durch Deprotonierung von Fluoren mit *n*BuLi und anschließender S_N-Reaktion des Fluorenylanions mit einem Alkylhalogenid
2.) Deprotonierung des 9-Alkylfluorens mit einer starken Base (*n*BuLi oder LDA), Reaktion des Anions mit dem entsprechenden Dialkylphosphinchlorid
3.) Protonierung des Phosphins mit HBF_4 und Isolation als luftstabiles Phosphoniumsalz

Auf diese Weise gelang die Darstellung siebzehn sterisch und elektronisch verschiedener Phosphine in hoher Reinheit (>99 %) und in Ausbeuten bis zu 90 %.

In situ gebildete Palladiumkomplexe der einzelnen Phosphine wurden auf ihre katalytische Aktivität in verschiedenen Kreuzkupplungsreaktionen mit Arylbromiden und Arylchloriden hin getestet. Zunächst erfolgten Screenings in organischen Lösemitteln. Bemerkenswerte Aktivitäten konnten in der Sonogashira-Kupplung festgestellt werden. Für die besten

Liganden konnten TONs von über 25000 bei der Kupplung elektronenreicher Bromaromaten festgestellt werden. Unter gleichen Bedingungen liegt die Aktivität der Fluorenylphosphine damit für diesen Reaktionstyp signifikant höher als bei den für ihre Leistungsfähigkeit bekannten Liganden P*t*Bu$_3$ (**M4**) oder Ad$_2$PBn (**M20**). Die hohe Katalysatoraktivität bestätigte sich auch bei Sonogashira-Kupplungen mit Chloraromaten. Hier genügte eine Katalysatorbeladung von 1 mol%, um sehr gute Ausbeuten zu erreichen. Weiterhin konnten die neuen Liganden erfolgreich in Buchwald-Hartwig-Aminierungen und Suzuki-Kupplungsreaktionen von Chlor- und Bromaromaten eingesetzt werden. Fluorenylphosphine mit längerem *n*-Alkylsubstituenten in 9-Fluorenylposition und sterisch anspruchsvollen Cyclohexylresten als direkte Phosphorsubstituenten konnten als die insgesamt aktivsten Liganden identifiziert werden.

Die hohe Variabilität der Fluorenylphosphine erlaubt die selektive und quantitative Monosulfonierung des Vertreters EtFluPCy$_2$ am fertigen Phosphoniumsalz. Durch die Einführung einer Sulfonsäuregruppe besitzt das sulfonierte Phosphin eine polare Phasenmarkierung. Dies ermöglicht die Bildung eines wasserlöslichen Pd-Komplexes und damit Katalysen in wässrigen Medien. Suzuki-Kreuzkupplungen diverser Arylhalogenide gelangen in reinem Wasser als Lösemittel mit 0.01-0.5 mol% Katalysatorbeladung bei milden Temperaturen. Die Kupplung von Chlorpyridinen oder Pyridinboronsäuren gelang mit signifikant niedrigerer Katalysatorbeladung als bis dato in der Literatur bekannt. Erfolgreiche Cu(I)-freie Sonogashira-Kupplungen von Bromaromaten in wässrigen Medien vervollständigen das erste Aktivitätsscreening der neuen Fluorenylphosphine.

FULL PAPER

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9-Fluorenylphosphines for the Pd-Catalyzed Sonogashira, Suzuki, and Buchwald–Hartwig Coupling Reactions in Organic Solvents and Water

Christoph A. Fleckenstein and Herbert Plenio*[a]

Abstract: The lithiation/alkylation of fluorene leads to various 9-alkyl-fluorenes (alkyl = Me, Et, *i*Pr, -Pr, $-C_{18}H_{25}$) in >95% yields, for which lithiation and reaction with R_2PCl (R = Cy, *i*Pr, *t*Bu) generates 9-alkyl, 9-PR_2-fluorenes which constitute electron-rich and bulky phosphine ligands. The in-situ-formed palladium–phosphine complexes ($[Na_2PdCl_4]$, phosphonium salt, base, substrates) were tested in the Sonogashira, Suzuki, and Buchwald–Hartwig reactions of aryl chlorides and aryl bromides in organic solvents. The Sonogashira coupling of aryl chlorides at 100–120°C leads to >90% yields with 1 mol% of Pd catalyst. The Suzuki coupling of aryl chlorides typically requires 0.05 mol% of Pd catalyst at 100°C in dioxane for quantitative product formation. To carry out "green" cross-coupling reactions in water, 9-ethylfluorenyldicyclohexylphosphine was reacted in sulphuric acid to generate the respective 2-sulfonated phosphonium salt. The Suzuki coupling of activated aryl chlorides by using this water-soluble catalyst requires only 0.01 mol% of Pd catalyst, while a wide range of aryl chlorides can be quantitatively converted into the respective coupling products by using 0.1–0.5 mol% of catalyst in pure water at 100°C. Difficult substrate combinations, such as naphthylboronic acid or 3-pyridylboronic acid and aryl chlorides are coupled at 100°C by using 0.1–0.5 mol% of catalyst in pure water to obtain the respective *N*-heterocycles in quantitative yields. The copper-free aqueous Sonogashira coupling of aryl bromides generates the respective tolane derivatives in >95% yield.

Keywords: Buchwald–Hartwig amination · palladium · phosphines · Sonogashira coupling · Suzuki coupling · water

Introduction

Trialkylphosphines with bulky substituents are highly useful ligands for palladium-complex catalysts in various types of cross-coupling reactions of the Suzuki,[1–11] Sonogashira,[12–21] Heck,[22–27] Buchwald–Hartwig amination[28–34] and ether formation,[35] Negishi,[36] Stille,[37–39] Hiyama,[40] Kumada,[41] α-arylation,[42,43] and carbonylation type.[44] The main reasons for the favorable catalytic properties of trialkylphosphine–palladium complexes are the electron-richness and the steric bulk of trialkylphosphine ligands, which favor the formation of low-coordinate and highly active Pd complexes, possibly of the L_1Pd type,[45–48] also observed with N-heterocyclic carbenes as Pd ligands in cross-coupling reactions.[49] Prominent examples of trialkyl phosphines are PCy_3, $PtBu_3$, and ligands of the Ad_2PR (Ad = 1-adamantyl, R = CH_2Ph, *n*Bu)[50] type. $PtBu_3$, especially, is highly useful; its utility for a wide range of different coupling reactions has been established.[51]

A significant disadvantage of Pd catalysts based on bulky trialkylphosphines, primarily $PtBu_3$, is the lack of flexibility in the design of ligands and catalysts. Detailed structural and electronic modifications (catalyst fine-tuning) are difficult to realize and this could be the reason why in cross-coupling chemistry this class of ligands was "leader of the pack" only about five years ago. Today numerous other specialized and more powerful catalysts, often based on phosphines and *N*-heterocyclic carbenes as ligands for Pd[49,52–61] are available. The advantages of a highly variable ligand backbone are demonstrated convincingly by the enormous success of Buchwald-type biphenyl-based phosphines,[62–64] as evidenced by the excellent performance of the respective Pd complexes in numerous coupling reactions.[65,66] The high level of sophistication concerning the fine-tuning of steric and electronic properties of such ligands was recently demonstrated by Buchwald et al. for Suzuki and amination reactions.[67–69]

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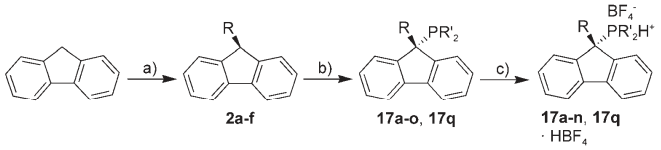
However, as crucial properties for good ligands, such as electron-richness and efficient σ-donation, are perfectly met in trialkyphosphines, we became interested in developing novel phosphines, lacking the disadvantages of P*t*Bu$_3$. In this vain, we want to demonstrate here the synthesis of a new class of trialkylphosphines based on the 9-fluorenyl group and the application of their Pd-complexes in Sonogashira, Suzuki, and Buchwald–Hartwig coupling reactions.



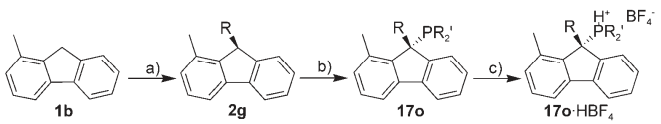
Scheme 1. Reagents and conditions: a) *n*BuLi, RX, THF, −60°C; b) *n*BuLi, R′$_2$PCl, Et$_2$O, −60°C; c) HBF$_4$·Et$_2$O.

Results and Discussion

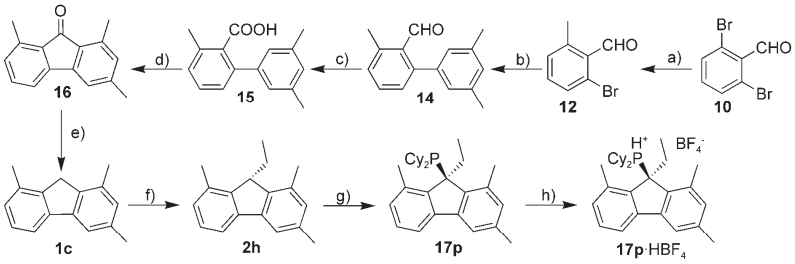
Synthesis of 9-fluorenyldialkylphosphines: The combination of 9-fluorenyl substituents with R$_2$P groups (Figure 1) in the corresponding phosphines appears to have numerous advantages: 1) a 9-fluorenyl group acts as an electron-rich alkyl substituent, 2) due to the formation of a resonance-stabilized anion, the 9-position is easily and selectively deprotonated and reacts smoothly as a soft nucleophile, 3) fluorenone is an umpoled synthon for the 9-fluorenyl group, 4) the close proximity of 6π-systems facilitates the stabilization of low-coordinate Pd species, 5) substituents at the 1,8-position allow the modulation of the steric bulk close the phosphorous donors, 6) the 2,7-positions allow the easy introduction of various functional groups.

Only a few fluorenyl-based trialkyphosphines have been described in the literature and none of them have been utilized in catalysis.[70,71] Simple (no additional substituents) 9-substituted fluorenylphosphines are prepared (Scheme 1) by reactions of the deprotonated fluorene (*n*BuLi) with various alkyl halides (MeI, EtI, *i*PrI, PhCH$_2$Cl, C$_{18}$H$_{37}$Br) to selectively introduce alkyl groups into the 9-position in virtually quantitative yield. This first alkylation step is essential as our very first catalysis screens had revealed that phosphines with 9-R = H produce Pd-complex catalysts with modest activities in cross-coupling reactions. For the introduction of the R$_2$P group, the 9-alkylated fluorene is again deprotonated with *n*BuLi and reacted with various chlorophosphines (*i*Pr$_2$PCl, Cy$_2$PCl) to result in the respective phosphines, which are conveniently converted into the respective phosphonium salts for easier storage and handling.[72]

To further increase the steric bulk close to the phosphine donor, the related 1-methyl- and 1,8-dimethyl-substituted fluorenes were synthesized, as described below (Schemes 2 and 3; Table 10).



Scheme 2. Reagents and conditions: a) *n*BuLi, EtI; b) *n*BuLi, Cy$_2$PCl; c) HBF$_4$·Et$_2$O.



Scheme 3. Reagents and conditions: a) 1,3-propanediol, ZrCl$_4$; *n*BuLi, MeI, H$_2$SO$_4$; b) Pd(OAc)$_2$, SIMES, Cs$_2$CO$_3$, 3,5-Me$_2$-C$_6$H$_3$B(OH)$_2$, dioxane; c) NaClO$_2$, H$_2$O$_2$; d) H$_2$SO$_4$; e) HI, red P, propionic acid; f) *n*BuLi, EtI, THF, −60°C; g) *n*BuLi, Cy$_2$PCl, Et$_2$O, −60°C; h) HBF$_4$·Et$_2$O.

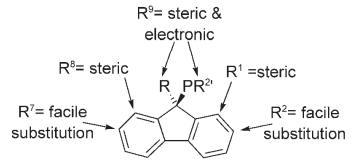


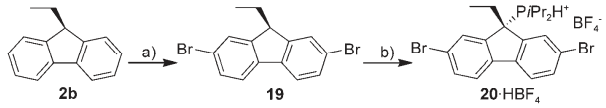
Figure 1. Variability of 9-fluorenylphosphines.

1-Methylfluorenone was prepared according to Mortier et al.,[73] deprotonated and reacted with ethyliodide to result in 1-methyl-9-ethylfluorene. Another sequence of deprotonation and quenching with Cy$_2$PCl gave the 9,9-disubstituted 1-methylfluorene, which was isolated as the respective phosphonium salt after protonation with HBF$_4$ (Scheme 2).

1,3,8-Trimethylfluorenone was prepared by a multistep reaction (Scheme 3). *Ortho* lithiation of 1,3-dibromobenzene by using the protocol of Servatovski et al. and subsequent

quenching with DMF resulted in 1,6-dibromobenzaldehyde,[74] which was protected as an acetal[75] and treated with *n*BuLi, followed by quenching the lithiated intermediate with methyliodide to yield the desired deprotected 1-bromo-6-methylbenzaldehyde in nearly quantitative yield. The Suzuki coupling of the bromo-aldehyde with 3,5-dimethylphenylboronic acid[76] afforded 3,3′,5′-trimethylbiphenylcarbaldehyde, which was converted into the respective carboxylic acid with $H_2O_2/NaClO_2$ by using the method of Dalcanale.[77] The resulting carboxylic acid gave 1,3,8-trimethylfluorenone in quantitative yield after condensation in concentrated sulfuric acid. By using the method of Carruthers,[78] the desired fluorene derivative was obtained by reduction of the fluorenone with HI and red phosphorous in propionic acid. Deprotonation of 1,3,8-trimethylfluorenone with *n*BuLi by using the standard protocol and quenching with ethyliodide gave the 9-ethylated fluorene derivative. Following the next deprotonation with *n*BuLi and reaction with Cy_2PCl, the respective 9-fluorenylphosphine was isolated as the phosphonium salt.

To demonstrate the variability of the 9-fluorenylphosphine chemistry, we have also synthesized a 2,7-dibromo derivative, which enables the easy introduction of additional functional groups at the 2,7-positions (Scheme 4).



Scheme 4. Reagents and conditions: a) bromine, $FeCl_3$, $CHCl_3$, 0 °C–RT; b) LDA, Et_2O, −60 °C, iPr_2PCl, HBF_4·Et_2O.

Pd complexes of 9-fluorenyldialkylphosphines in the Sonogashira reaction: As a first test of the performance of the various Pd 9-fluorenylphosphine complexes, we determined the ton (turnover number) for the Sonogashira cross-coupling of phenylacetylene and 4-bromotoluene, applying the conditions described previously by us (Table 1).[17] In this first screen, the nature of the groups 9-R and 9-PR'_2 were varied. There are a number of phosphines (9-R = H, Ph, *i*Pr, *t*Bu) that display ton of smaller than 1000. This is significantly smaller than that of our reference phosphine Ad_2PBn (ton = 3200). Consequently, these phosphines were excluded from future catalytic test reactions. There are several phosphines for which the performance is comparable or superior to that of our reference system. The best 9-fluorenylphosphines are characterized by an unbranched alkyl group (R = Me, Et, etc.) at the 9-position, -P*i*Pr_2 or -PCy_2 units at the phosphorous atom.

It is known that sp^2–CH bonds close to the binding site of palladium can easily undergo CH-activation reactions,[79,80] which is less likely with sp^3–CH bonds.[68] With this in mind and with a view to further increasing the steric bulk of the phosphines, we synthesized two fluorenyl dialkylphosphines with methyl groups in the 1- or in the 1,8-position. To our

Table 1. Primary Sonogashira screen for the reaction of phenylacetylene and 4-bromotoluene by utilizing various phosphines.

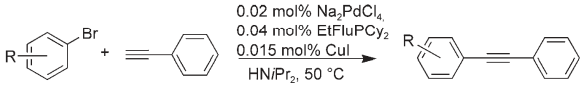
Phosphine	ton[a,b]
C_{18}FluPCy_2 (**17i**)	5900
EtFluPCy_2 (**17c**)	5600
MeFluPCy_2 (**17a**)	5600
C_{18}FluP*i*Pr_2 (**17j**)	5500
Ad_2PBn	3600
MeFluP*i*Pr_2 (**17b**)	3500
EtFluP*i*Pr_2 (**17d**)	3200
1-Me-9-EtFluPCy_2 (**17o**)	2600
*i*PrFluPCy_2 (**17e**)	906
1,3,8-Me_3EtFluPCy_2 (**17p**)	850
*i*PrFluP*i*Pr_2 (**17f**)	500
HFluP*t*Bu_2 (**17h**)	330
PhFluP*i*Pr_2 (**17q**)	250

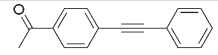
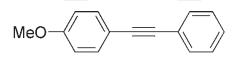
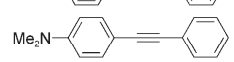
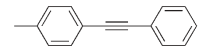
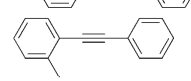
[a] 4-Bromotoluene (10 mmol), phenylacetylene (11 mmol), *i*Pr_2NH (10 mL), 50 °C, 24 h. Catalyst: $[Na_2PdCl_4]$/ligand/CuI 4:8:3, catalyst mixture in *i*Pr_2NH_2Br, max. ton = 15000. [b] Average of two runs. Determined by the mass of the isolated ammonium salt.

surprise, the performance of the 1,8-Me_2-substituted 9-fluorenylphosphines **17p** is poor (ton = 850), while the related compound with a single methyl group at the 1-position shows a good performance (ton = 2600), even though it is not among the top performers. However, given the significantly increased effort required for the synthesis of the 1- and the 1,8-substituted fluorenes, we did not consider it worthwhile to study the performance of these phosphines in more detail.

Among the best phosphines in Table 1, EtFluPCy_2 **17c** was tested for the conversion of a number of aryl bromides (Table 2). Quantitative yields are possible with various acti-

Table 2. Sonogashira coupling of various aryl bromides with phenylacetylene[a] by using EtFluPCy_2·HBF_4.



Entry	Aryl bromide	Product	*t* [h]	Yield [%][b]
1	4-bromoacetophenone		3	≥99
2	4-bromoanisol		24	≥99
3	4-bromodimethylaniline		24	≥99
4	4-bromotoluene		24	≥99
5	2-bromotoluene		24	95

[a] Aryl bromide (10 mmol), phenylacetylene (11 mmol), HN*i*Pr_2 (10 mL), 50 °C, 24 h. Catalyst: $[Na_2PdCl_4]$ (0.02 mol%), phosphine (0.04 mol%), CuI (0.015 mol%), catalyst mixture in *i*Pr_2NH_2Br. [b] Average of two runs, determined by GC analysis (hexadecane as an internal standard) and by the mass of the isolated ammonium salt. Both analytical methods gave similar results.

vated and deactivated aryl bromides when applying 0.02 mol% of Pd complex. To test the limits of catalytic performance, the catalyst concentration was decreased to 0.0033% (Table 3). Even at such low catalyst concentrations,

Table 3. Sonogashira coupling of aryl bromides. Determination of ton.[a]

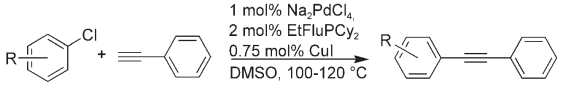
Entry	Aryl bromide	Acetylene	R_3PH^+[b]	Pd [mol%]	t [h]	Yield [%][c]	ton
1	bromobenzene	phenylacetylene	a	0.0033	16	81	24300
2	bromobenzene	phenylacetylene	b	0.0033	16	88	26400
3	2-bromotoluene	phenylacetylene	a	0.0033	16	83	24900
4	2-bromo-*m*-xylene	phenylacetylene	a	0.0067	16	57	8550
5	2-bromo-benzotrifluoride	phenylacetylene	b	0.0033	16	51	15300
6	4-bromoanisol	phenylacetylene	c	0.0033	20	41	12200
7	4-bromoanisol	phenylacetylene	a	0.0033	20	78	23300
8	4-bromoanisol	phenylacetylene	b	0.0033	20	84	25200
9	4-bromoanisol	phenylacetylene	d	0.0033	20	43	12600

[a] Aryl bromide (10 mmol), acetylene (11 mmol), HN*i*Pr$_2$ (10 mL), 80°C, 24 h. Catalyst: [Na_2PdCl_4]/phosphonium salt/CuI 4:8:3, catalyst mixture in *i*Pr$_2$NH·HBr. [b] Ligand: a: MeFluP*i*Pr$_2$ (**17b**); b: EtFluP*i*Pr$_2$ (**17d**); c: MeFluPCy$_2$ (**17a**); d: *i*PrFluP*i*Pr$_2$ (**17f**). [c] Average of two runs.

deactivated substrates can be converted in more than 80% yield with ton around 8.500 for sterically hindered substrates and up to 25.000 with deactivated substrates (4-bromoanisol). The turnover frequencies (tof) for two Sonogashira reactions applying MeFluP*i*Pr$_2$ were determined at 80°C: 2-bromotoluene and phenylacetylene at 0.0033 mol% Pd catalyst concentration yield tof of 3600 h^{-1}; the analogous reaction with 4-bromoanisol gives tof of 2650 h^{-1}.

Finally, the Sonogashira coupling of phenylacetylene with several aryl chlorides was tested (Table 4). Excellent conver-

Table 4. Sonogashira reactions with aryl chlorides.[a]



Entry	Aryl chloride	T [°C]	t [h]	Yield [%][b]
1	4-chloroanisol	110	16	43, 44,[c] 47,[d] 23[e]
2	4-nitrochlorobenzene	100	12	88
3	4-chloroacetophenone	100	12	94
4	4-CF_3-chlorobenzene	100	12	92
5	chlorobenzene	120	16	87
6	4-chlorotoluene	120	16	91
7	4-chloroanisol	120	20	73

[a] Aryl chloride (1.5 mmol), phenylacetylene (2.1 mmol), Na_2CO_3 (3 mmol), DMSO (5 mL), catalyst: 1 mol% [Na_2PdCl_4]/ligand/CuI 4:8:3; phosphonium salt: MeFlu*i*Pr$_2$·HBF_4 (**17b**·HBF_4). Reaction conditions have not been optimized. [b] Average of two runs. Purified by chromatography through a short silica pad. Eluent: cyclohexane/ethyl acetate 100:2. [c] Ligand: EtFluPCy$_2$ (**17c**). [d] Ligand: BnFluPCy$_2$ (**17k**). [e] Ligand: Ad$_2$PBn.

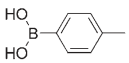
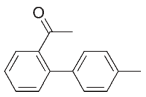
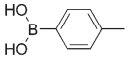
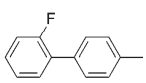
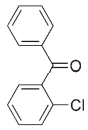
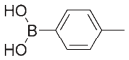
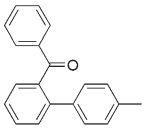
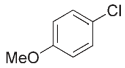
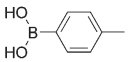
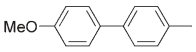
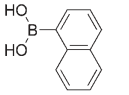
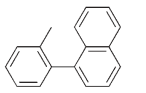
sions of the reactants were observed for all substrates at 100–120°C with 1 mol% of catalyst. Again, the 9-fluorenylphosphine-based palladium catalysts compare favorably with other catalytic systems described by us and by others for the conversion of aryl chlorides.[14,19,81–85]

Pd complexes of 9-fluorenyldialkylphosphines in the Suzuki reaction: We first tested Pd complexes of several phosphines, EtFluPCy$_2$ **17c**, BnFluPCy$_2$ **17k**, *i*PrFluPCy$_2$ **17e**, and MeFluP*i*Pr$_2$ **17b**, in the Suzuki coupling. In the reaction of 4-chloroacetophenone with 4-tolylboronic acid by using 0.5 mol% [Na_2PdCl_4] and 1 mol% phosphonium salt with Cs_2CO_3 in dioxane at 80°C, the following yields were observed: **17c** (77%), **17k** (13%), **17e** (5%), and **17b** (21%). Again, the phosphine with a 9-Et and the 9-PCy$_2$ group is the top performer in this series. It is interesting to observe that too much bulk at the 9-position (*i*Pr, Bn) appears to be detrimental for the coupling reactions (Table 5), while too little bulk of substituents directly attached to the phosphorous atom (9-P*i*Pr$_2$) is not favorable. An amount of 0.05 mol% of catalyst is sufficient to reach full conversion during 24 h; only 4-chloroanisol requires 0.1 mol% of catalyst to reach full conversion.

Pd complexes of 9-fluorenyldialkylphosphines in the Buchwald–Hartwig reaction: To demonstrate the broad applicability of the fluorenyl-based phosphines for coupling reactions, we carried out a few test reactions for the amination of aryl bromides and chlorides.[28,34,66,86] When applying the conditions recently reported by Beller et al. without further optimization,[63] the screening of several fluorenyldialkylphosphines in the reaction of 4-chlorotoluene with 3,5-dimethylaniline revealed EtFluPCy$_2$ as the most active ligand for palladium (Table 6, entry 1). Typical catalyst loadings of between 0.1–0.5 mol% Pd were applied at 120°C by using NaO*t*Bu as the base in toluene (Table 6). Overnight reactions of various aryl bromides gave quantitative conversion of different amines (aniline, morpholine, α-methylbenzylamine). Activated and nonactivated aryl chlorides were converted into the respective anilines under the same conditions in quantitative yields.

Sulfonation of 9-ethylfluorenyldicyclohexylphosphine and the catalytic activity of the respective Pd complexes in the Sonogashira and the Suzuki coupling in water: Water is a cheap, inflammable, and nontoxic solvent from which organic products are easily separated. It is therefore an attractive target to render palladium–phosphine complexes water-soluble in order to allow cross-coupling reactions in this "green" solvent.[87,88] Only a few examples of aqueous Suzuki coupling of aryl chlorides have been described, notable in this respect are recent publications by Buchwald et al.[89,90] and Fu et al.[11] who report on the facile Suzuki coupling in water and water/dioxane for a broad range of substrates.[4,91–93] Consequently, to render the 9-fluorenylphos-

Table 5. Suzuki reaction with aryl chlorides.[a]

Entry	Aryl chloride	Boronic acid	Product	Catalyst [mol%][b]	t [h]	Conversion [%][c]
1				0.5	2	≥99
				0.05	24	≥99
2				0.5	2	≥99
				0.05	24	≥99
3				0.5	2	≥99
				0.05	24	≥99
4				0.5	5	≥99
				0.1	20	≥99
				0.05	24	65
5				0.5	5	≥99
				0.05	24	≥99

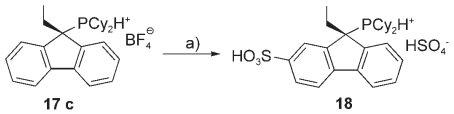
[a] Aryl chloride (1 mmol), boronic acid (1.5 mmol), Cs_2CO_3 (2.0 mmol), dioxane (5 mL), 100 °C, reaction conditions and the amount of catalyst have not been optimized. [b] Catalyst: [Na_2PdCl_4]/ligand 1:2, ligand: Et-FluPCy$_2$ (**17c**). [c] Average of two runs, determined by GC analysis using hexadecane as an internal standard.

phines water soluble, the aromatic ring was sulfonated by treatment of the phosphonium salt **17c** with concentrated sulphuric acid, resulting in the formation of the respective 2-sulfonated fluorene in 77% yield (Scheme 5).

We studied a range of different aryl bromides and aryl chlorides in Suzuki coupling reactions by using 4-tolueneboronic acid, 1-naphthylboronic acid, and 3-pyridylboronic acids (Table 7). Aryl bromides react smoothly at room temperature when using 0.1 mol% of catalyst to form the coupling product in quantitative yield, while a sterically demanding substrate (1-bromo-2,6-dimethylbenzene) requires 1 mol% and overnight reaction at the same temperature. A variety of bases (NaOH, K_2CO_3, Cs_2CO_3, K_3PO_4) were used, significant differences in the outcome of the coupling reaction were not observed and only KF gave poor results in aqueous Suzuki reactions. The addition of a surfactant (Labrasol)[94] leads to slightly improved yields in some cases. The aryl chlorides listed in Table 7 are quantitatively converted by using between 0.1–1 mol% of catalyst during 1–2 h at 100 °C. Activated aryl chlorides, such as 4-chlorobenzonitrile (entry 11), require only 0.1 mol% of catalyst to produce the coupling product in quantitative yield within 30 min. Coupling reactions of 1-naphthylboronic acid (Table 7, entries 19, 20, 23) occur at elevated temperatures with 0.5 mol% of catalyst to produce the respective coupling products in nearly quantitative yields.

N-Heterocycles, such as pyridines, are an important class of substances for pharmaceutical applications.[95] Due to the coordinating nature of pyridines such compounds are a challenging class of substrates in the Suzuki coupling of aryl chlorides.[68,96–98] Recently, Fu et al. and Buchwald et al. reported catalysts that are able to couple various substituted pyridylboronic acids and aryl chlorides in 90–95% yield by using 2–3 mol% of Pd catalyst at 90–100 °C during 24 h in *n*-butanol or in dioxane/water as solvents.[11,68] Encouraged by the high activity of the Pd complexes of the sulfonated fluorenene **18**, we also tried coupling reactions of pyridylboronic acid in the aqueous Suzuki coupling (Table 7, entries 24–28). Activated aryl chlorides (2-CF_3-chlorobenzene, Table 7, entry 26) require only 0.1 mol% of catalyst at 100 °C for quantitative conversion, while nonactivated (chlorobenzene) aryl chlorides work with 0.5 mol% (entry 25). It is remarkable that even pyridyl chlorides can be coupled with pyridyl boronic acids to result in the formation of the respective bipyridines by applying 0.5 mol% of Pd catalyst (entries 27, 28), even at 0.1 mol%, a respectable 43% yield is observed. It is obvious from our experiments carried out in pure water as the solvent that the catalysts reported appear to be the most active ones reported so far for this class of challenging substrates. In conclusion, we were able to demonstrate the excellent activity of the sulfonated **18** in the aqueous Suzuki coupling for a wide range of different substrates.

We also studied the copper-free Sonogashira coupling (also referred to as the Cassar–Heck coupling) by using various aryl bromides in water/isopropanol; yields in excess of 95% are observed for a variety of substrate combinations (Table 8),[18,99–102] while aryl chlorides could not be reacted under these conditions.



17 c 18

Scheme 5. Reagents and conditions: a) H_2SO_4, 40 °C.

Conclusions

The 9-fluorenylphosphines described here, constitute a versatile new class of phosphorous ligands, for which the palladium complexes were shown to be high activity catalysts for the Buchwald–Hartwig, Sonogashira, and Suzuki coupling of

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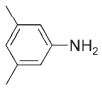
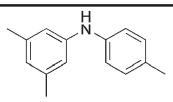
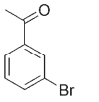
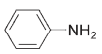
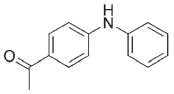
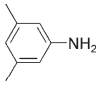
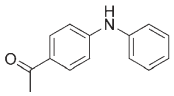
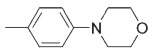
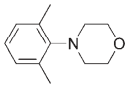
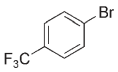
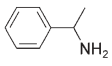
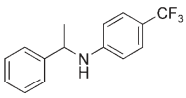
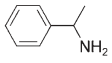
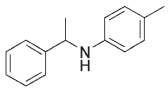
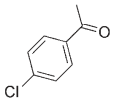
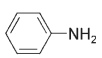
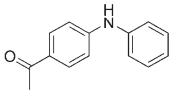
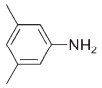
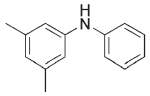
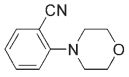
Table 6. Buchwald–Hartwig amination[a] of aryl bromides and chlorides.

Entry	Aryl halide	Amine	Product	Catalyst [mol%]	t [h]	Conversion [%][b]
1				0.5	12	16
				0.5[c]	12	<5
				0.5[d]	12	<5
				0.5[e]	12	<5
2				0.1	3	≥99
3				0.5	2	≥99
4				0.5	2	≥99
5				0.5	6	91
6				0.25	2	≥99
7				0.5	2	≥99
8				0.5	12	≥99
9				0.5	12	≥99
10				0.5	12	48

[a] Toluene (5 mL), aryl halide (5 mmol), amine (6 mmol),NaO*t*Bu (6 mmol), Pd/ligand 1:2, phosphonium salt: EtFluPCy$_2$·HBF$_4$ (**17c**·HBF$_4$), 120°C, reaction conditions have not been optimized. [b] Average of two runs, determined by GC analysis using hexadecane as internal standard. [c] Ligand: PhFluP*i*Pr$_2$ (**17q**). [d] Ligand: *i*PrFluP*i*Pr$_2$ (**17f**). [e] Ligand: BnFluPCy$_2$ (**17k**).

aryl chlorides. Fluorenyl-based phosphines are trialkylphosphines with excellent electron-donating properties and large steric bulk similar to P*t*Bu$_3$. However, in contrast to the latter ligand, the fluorenylphosphines can be modified easily at various positions of the fluorene to allow the design of numerous modified catalysts. The catalytic performance of the Pd complexes of the first generation of 9-alkyl, 9-dialkylphosphinofluorenes reported here is already impressive. Aryl chlorides can be coupled in quantitative yields in the Sonogashira, Suzuki, and Buchwald–Hartwig reaction in organic solvents or in water by using between 0.01 and 1 mol% of catalyst for the various reactions and substrates listed here. Noteworthy, are the excellent activities of Pd complexes of sulfonated 9-dialkylphosphinofluorenes for the Suzuki coupling in pure water with a wide range of substrates, including sterically demanding or heterocyclic boronic acids, which exceed those recently reported by others for the notoriously difficult synthesis of nitrogen-containing heterocycles.

Experimental Section

General experimental: All chemicals were purchased as reagent grade from commercial suppliers and used without further purification, unless otherwise noted. THF was distilled over potassium and benzophenone under an argon atmosphere, diethyl ether was distilled over sodium/potassium alloy and benzophenone under an argon atmosphere. Diisopropylamine was dried over potassium hydroxide, dioxane was dried over calcium hydride. Proton (^{1}H NMR), carbon (^{13}C NMR) and phosphorus (^{31}P NMR) NMR spectra were recorded on Bruker DRX 500 at 500, 125.75, and 202.46 MHz, respectively or on Bruker DRX 300 at 300 and 75.07 MHz, respectively. The chemical shifts are given in parts per million (ppm) on the delta scale (δ) and are referenced to TMS (δ=0 ppm), ^{1}H NMR and 65% aq H_3PO_4 (δ=0 ppm), ^{31}P NMR. Abbreviations for NMR data: s=singlet, d=doublet, t=triplet, q=quartet, dd=doublet of doublets, dt=doublet of triplets, dq=doublet of quartets, tt=triplet of triplets, m=multiplet. IR spectra were recorded on Perkin–Elmer 1600 series FTIR. Mass spectra were recorded on a Finigan MAT 95 magnetic sector spectrometer. TLC was performed by using Fluka silica gel 60 F_{254} (0.2 mm) on aluminum plates. Silica-gel columns for chromatography were prepared with E. Merck silica gel 60 (0.063–0.20 mesh ASTM).

General procedure for the preparation of 9-substituted fluorenes (Table 9): *n*BuLi (40 mmol, 2.5 M in hexane) was added at −60°C to a solution of 9*H*-fluorene (30 mmol) in dry THF (60 mL). The solution immediately turned brownish and was stirred for 1.5 h at RT. After cooling to −60°C again, the reaction mixture was quenched with alkylhalide (45 mmol, 1.5 equiv), stirred for 10 min at −60°C, then for an additional 2 h at RT. Water (100 mL) was added to the reaction mixture which was then extracted with diethyl ether (3×100 mL). The combined organic phases were subsequently washed with an aqueous solution of $Na_2S_2O_3$, brine, and dried over $MgSO_4$. After filtration and removal of the volatiles under vacuum, the crude product was purified by filtration on a short silica-gel pad (5 cm, eluent: cyclohexane) and concentrated under vacuum, resulting in the pure 9-substituted fluorenes typically in near quantitative yield.

9-Methylfluorene (2a): Fluorene (**1a**) (15.0 g, 90.4 mmol), *n*BuLi (48.1 mL, 120 mmol, 2.5 M in hexane), iodomethane (19.3 g, 136 mmol).

Table 7. Suzuki coupling of aryl bromides and aryl chlorides in water.

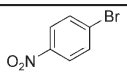
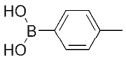
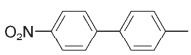
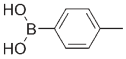
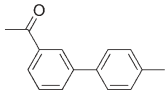
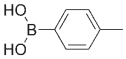
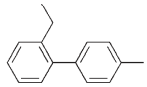
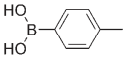
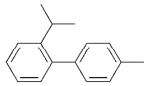
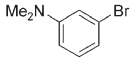
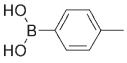
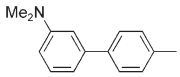
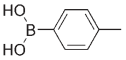
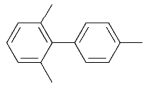
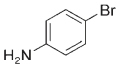
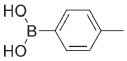
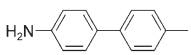
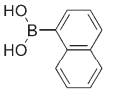
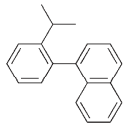
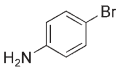
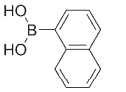
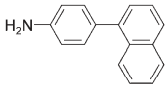
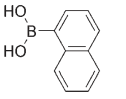
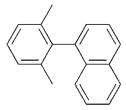
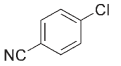
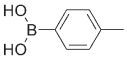
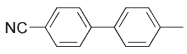
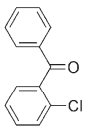
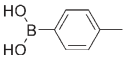
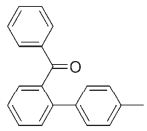
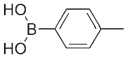
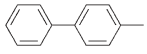
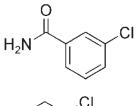
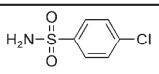
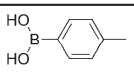
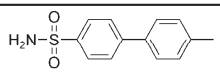
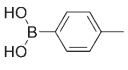
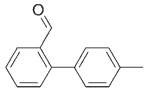
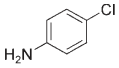
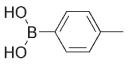
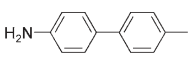
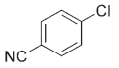
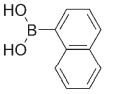
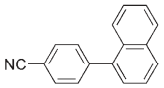
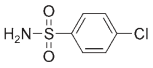
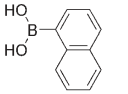
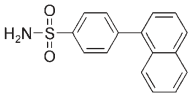
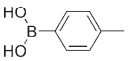
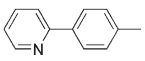
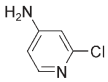
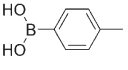
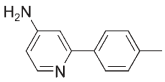
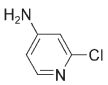
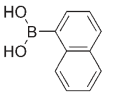
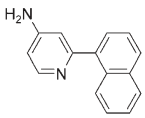
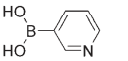
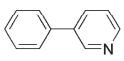
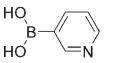
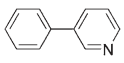
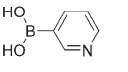
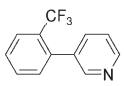
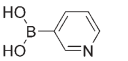
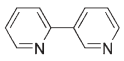
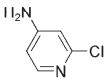
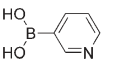
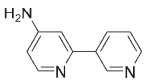
Entry	Halide	Boronic acid	Product	Pd [mol%]	Conditions	Yield [%][f]
1				0.1	RT, 20 h	≥99
				0.01	100°C, 2 h	≥99
				0.005	100°C, 3.5 h	≥99
2				0.5	90°C, 45 min	≥99
				0.5	90°C,30 min[a]	≥99
3				0.5	50°C, 1.5 h	≥99
4				0.5	50°C, 4 h	≥99
5				0.5	50°C, 1.5 h	≥99
6				1	RT, 20 h	≥99
7				0.25	RT, 3 h	≥99
				0.1	RT, 2.5 h	50
				0.1	RT, 2.5 h[a]	66
8				1	100°C, 20 h	≥99
9				0.5	65°C, 20 h	≥99
10				1	90°C, 20 h	≥99
				0.05	100°C, 2 h	≥99
				0.1	100°C, 30 min	≥99
				1	40°C, 10 h	≥99
11				1	RT, 20 h[a]	≥99
				0.1	100°C, 45 min[b]	≥99
				0.1	100°C, 1 h[c]	≥99
				0.1	100°C, 1 h[d]	≥99
				0.1	100°C, 25 min[e]	≥99
12				0.5	90°C, 4 h	92
				0.5	90°C, 4 h[a]	98
13				0.5	100°C, 2 h	≥99
				1	RT, 20 h[a]	≥99
14				0.5	100°C, 2.5 h[a]	≥99
				1	RT, 20 h[a]	≥99
15				0.5	100°C, 90 min	≥99

Table 7. (Continued)

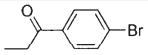
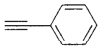
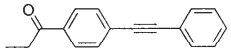
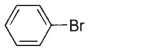
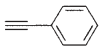
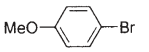
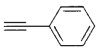
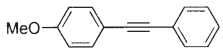
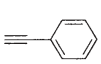
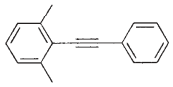
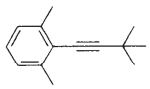
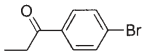
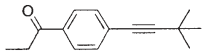
Entry	Halide	Boronic acid	Product	Pd [mol%]	Conditions	Yield [%][f]
16				1	100°C, 24 h	≥99
17				1 0.5	90°C, 30 min RT, 4 h	≥99 ≥99
18				0.5	90°C, 20 h	74
19				0.5	65°C, 20 h	80
20				0.5	90°C, 20 h	≥99
21				0.5	100°C, 12 h[a]	≥99
22				0.5	100°C, 12 h[a]	≥99
23				0.5	100°C, 12 h[a]	≥99
24				0.1	100°C, 12 h[a]	≥99
25				0.5	100°C, 12 h[a]	≥99
26				0.1	100°C, 12 h[a]	≥99
27				0.5	100°C, 12 h[a]	≥99
28				0.5 0.1	100°C, 20 h[a] 100°C, 20 h[a]	≥99 43
29				1.0	100°C, 20 h[a]	97
30				1.0 0.5	100°C, 20 h[a] 100°C, 20 h[a]	96 90

Reaction conditions: aryl halide (1.0 equiv), boronic acid (1.2 equiv), K_2CO_3 (3.2 equiv), degassed water (4 mL, mmol^{-1}), cat. [Na_2PdCl_4], ligand **18**, ligand/Pd 2:1. Reaction times and temperatures were not optimized. [a] Additive: Labrasol (0.05 mL). [b] Aryl halide (1 equiv), boronic acid (1.2 equiv), $CsCO_3$ (3.2 equiv). [c] Aryl halide (1 equiv), boronic acid (1.2 equiv), KF (3.2 equiv). [d] Aryl halide (1 equiv), boronic acid (1.2 equiv), NaOH (3.2 equiv). [e] Aryl halide (1 equiv), boronic acid (1.2 equiv), K_3PO_4 (3.2 equiv). [f] Average of two runs, determined by GC analysis using hexadecane as an internal standard.

Product **2a** was isolated as a yellowish waxy solid (16.2 g, quant.). The analytical data were identical to those in the literature.[103] ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.74 (d, ^3J=7.5 Hz, 2H; Ar), 7.49–7.48 (m, 2H; Ar), 7.34–7.28 (m, 4H; Ar), 3.92 (q, ^3J=7.5 Hz, 1H; 9*H*Flu), 1.50 ppm (d, ^3J=5.5, 7.5 Hz, 3H; CH_3); ^{13}C{^{1}H} NMR (125.77 MHz, $CDCl_3$): δ= 149.4, 141.0, 127.4 (2×), 124.5, 120.3, 42.9, 18.6 ppm.

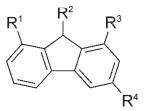
9-Ethylfluorene (2b): Fluorene (**1a**) (5.0 g, 30.1 mmol), *n*BuLi (16 mL, 40 mmol, 2.5 M in hexane), iodoethane (7.04 g, 45.1 mmol). Product **2b**

Table 8. Sonogashira reaction of aryl bromides in an aqueous system.[a]

Entry	Aryl bromide	Acetylene	Product	t [h]	Conversion [%][b]	Yield [%][c]
1				1	≥99	97
2				1.5	≥99	98
3				2	≥99	95
4				4	≥99	95
5				4	≥99	94
6				4	≥99	95

[a] Aryl bromide (1 mmol), acetylene (1.2 mmol), Cs_2CO_3 (1.5 mmol), $[Na_2PdCl_4]$ (1 mol%), ligand ((9-ethyl-2-sulfonic acid-fluorenyl)dicyclohexyl phosphonium HSO_4^-, 2 mol%); 9-SO_3H-EtFluPCy$_2$-H_2SO_4 (**18**), H_2O/isopropanol (4 mL, 1:1), 100°C. Reaction times and temperatures were not optimized. [b] Average of two runs, determined by GC analysis using hexadecane as an internal standard. [c] Average of two runs. Purified by column chromatography (silica gel, eluent: cyclohexane/ethyl acetate 10:1).

Table 9. 9-Substituted fluorenes.



Compound	R^1	R^2	R^3	R^4
2a	H	Me	H	H
2b	H	Et	H	H
2c	H	*i*Pr	H	H
2d	H	*n*Pr	H	H
2e	H	C_{18}	H	H
2f	H	Bn	H	H
2g	Me	Et	H	H
2h	Me	Et	Me	Me

was isolated as yellow oil (5.7 g, 97%). Analytical data were identical to those in the literature.[104] ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.73 (d, ^3J=10.0 Hz, 2H; Ar), 7.50–7.48 (m, 2H; Ar), 7.36–7.27 (m, 4H; Ar), 3.94 (t, ^3J=6.0 Hz, 1H; 9*H*Flu), 2.07 (dq, ^3J=5.5, 7.0 Hz, 2H; CH_2), 0.71 ppm (t, ^3J=7.5 Hz, 3H, CH_3); ^{13}C{^{1}H} NMR (125.77 MHz, $CDCl_3$): δ=147.2, 141.3, 126.8, 126.7, 124.3, 119.7, 48.5, 25.7, 9.7 ppm.

9-Isopropylfluorene (2c): Fluorene (**1a**) (15.0 g, 90.4 mmol), *n*BuLi (48.1 mL, 120 mmol, 2.5 M in hexane), 2-iodopropane (14.0 mL, 139.6 mmol). Product **2c** was isolated as a yellowish solid (18.7 g, quant.). The analytical data were identical with these to be found in the literature.[103] ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.73 (d, ^3J=7.5 Hz, 2H; Ar), 7.52–7.51 (m, 2H; Ar), 7.37–7.25 (m, 4H; Ar), 3.91 (d, ^3J=3.0 Hz, 1H; 9*H*Flu), 2.59–2.52 (m, 1H; C*H*), 0.84 ppm (d, ^3J=7.0 Hz, 6H; CH_3); ^{13}C{^{1}H} NMR (125.77 MHz, $CDCl_3$): δ=146,7, 142.1, 127.3, 127.1, 125.2, 120.0, 54.2, 32.6, 19.5 ppm (CH_3, 2×).

9-*n*-Propylfluorene (2d): Fluorene (**1a**) (15.0 g, 90.4 mmol), *n*BuLi (48.1 mL, 120 mmol, 2.5 M in hexane), 1-iodopropane (20.8 g, 122.3 mmol). Product **2d** was isolated as a yellowish solid (18.6 g, quant.). The analytical data were identical to those found in the literature.[105] ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.73 (d, ^3J=7.0 Hz, 2H; Ar), 7.51–7.49 (m, 2H; Ar), 7.36–7.27 (m, 4H; Ar), 3.97 (t, ^3J=6.0 Hz, 1H; 9*H*Flu), 1.99–1.94 (m, 2H; CH_2), 1.27–1.19 (m, 2H; CH_2), 0.86 ppm (t, ^3J=7.5 Hz, 3H; CH_3); ^{13}C{^{1}H} NMR (125.77 MHz, $CDCl_3$): δ=147.7, 141.1, 126.8, 126.7, 124.4, 119.8, 47.4, 35.4, 19.0, 14.4 ppm.

9-*n*-Octadecylfluorene (2e): Fluorene (**1a**) (7.0 g, 42.1 mmol), *n*BuLi (17.35 mL, 43.4 mmol, 2.5 M in hexane), 1-bromooctadecane (14.53 g, 43.6 mmol). Following the usual workup, **2e** was isolated as a white solid (15.5 g, 88%). R_f=0.73 (cyclohexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.76–7.73 (m, 2H; Ar), 7.52–7,49 (m, 2H; Ar), 7.38–7,27 (m, 4H; Ar), 3.96 (t, ^3J=6.0 Hz, 1H; 9*H*Flu), 3.02–1.95 (m, 2H; CH_2), 1.31–1.14 (m, 32H; CH_2), 0.88 ppm (t, ^3J=6.6 Hz, 3H; CH_3); ^{13}C{^{1}H} NMR (75.42 MHz, $CDCl_3$): δ=147.7, 141.1, 126.8, 126.7, 124.3, 119.8, 47.5, 33.1, 31.9, 30.0, 29.7 (CH_2, 7×), 29.6 (CH_2, 3×), 29.4, 29.3, 25.7, 22.7, 14.1 ppm.

9-Benzylfluorene (2f): Fluorene (**1a**) (19.0 g, 114 mmol), *n*BuLi (54.9 mL, 137 mmol, 2.5 M in hexane), benzylchloride (17.03 mL, 148 mmol). After the usual workup, **2a** was isolated and recrystallized from heptane to give a white solid (25.8 g, 88.4%). The analytical data were identical to those in the literature.[106] ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.72 (d, ^3J=8 Hz, 2H; Ar), 7.37–7.13 (m, 11H; Ar), 4.22 (t, ^3J=7.5 Hz, 9H; Flu), 3.10 ppm (d, ^3J=7.5 Hz, 2H; CH_2); ^{13}C{^{1}H} NMR (125.77 MHz, $CDCl_3$): δ=146.8, 140.8, 139.8, 129.5, 128.3, 127.1, 126.6, 126.4, 124.8, 119.8, 48.7, 40.1 ppm.

1-Methyl-9-ethylfluorene (2g): Fluorene (**1b**) (3.01 g, 16.7 mmol), *n*BuLi (8.06 mL, 20 mmol, 2.5 M in hexane), 1-iodoethane (3.39 g, 21.7 mmol). Product **2h** was isolated to give a colorless oil (3.33 g, 95%). ^{1}H NMR (500 MHz, [D$_6$]acetone): δ=7.79–7.77 (m, 1H; Ar), 7.64 (d, ^3J=7.5 Hz, 1H; Ar), 7.55–7.53 (m, 1H; Ar), 7.34–7.24 (m, 3H; Ar), 7.10–7.08 (m, 1H; Ar), 4.11 (t, ^3J=4.5 Hz, 1H; 9*H*Flu), 2.46 (s, 3H; CH_3), 2.26–2.20 (m, 2H; CH_2), 0.35 ppm (t, ^3J=7.5 Hz, 3H; CH_3); ^{13}C{^{1}H} NMR (125.75 MHz, [D$_6$]acetone): δ=148.0, 145.4, 142.6, 142.4, 135.2, 129.4, 128.0, 127.7, 127.6, 124.9, 120.4, 118.1, 48.5, 24.3, 19.2, 8.3 ppm.

1,3,8-Trimethyl-9-ethylfluorene (2h): Fluorene (**1c**) (1.2 g, 5.77 mmol), *n*BuLi (3.0 mL, 2.5 M in hexane, 7.5 mmol), 1-iodoethane (1.35 g, 8.65 mmol). Product **2h** was isolated to give a white solid (1.36 g, quant.). ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.55 (d, ^3J=7.2 Hz, 1H; Ar), 7.40 (s, 1H; Ar), 7.27 (t, ^3J=7.2 Hz, 1H; Ar), 7.08 (d, ^3J=7.5 Hz, 1H; Ar), 6.93 (s, 1H; Ar), 4.23 (t, ^3J=4.2 Hz, 1H; 9*H*Flu), 2.49 (s, 3H; CH_3), 2.46 (s, 3H, CH_3), 2.43 (s, 3H, CH_3), 2.30 (dq, ^3J=4.2 Hz, 2H; CH_2), 0.19 ppm (t, ^3J=7.8 Hz, 3H; CH_3); ^{13}C{^{1}H} NMR (75.4 MHz, $CDCl_3$): δ=145.3, 142.1, 136.7, 134.1, 133.7, 129.6, 128.5, 127.0, 118.0, 117.2, 46.7, 21.5, 21.1, 19.2, 19.1, 7.2 ppm.

1-Methylfluorene (1b): 1-Methylfluoren-9-one (**8**) (6.8 g, 35 mmol) was dissolved in propionic acid (450 mL). Red phosphorus (7.4 g) and concentrated HI (100 mL) were added and the reaction mixture was refluxed for 24 h. Quantitative conversion was shown by TLC. The reaction mixture was diluted with water (500 mL), neutralized with NaOH, and extracted with Et_2O (4×125 mL). The combined organic layers were washed with brine (2×125 mL), dried over $MgSO_4$, filtered, and the volatiles removed in vacuo to afford 6.1 g (97%) of **1b** as a white solid. The analytical data were consistent with the literature.[107,108] ^{1}H NMR (500 MHz, [D$_6$]acetone): δ=7.82 (d, ^3J=8.0 Hz, 1H; Ar), 7.67 (d, ^3J=7.5 Hz, 1H; Ar), 7.58–7.56 (m, 1H; Ar), 7.36–7.34 (m, 1H; Ar), 7.30–7.26 (m, 2H; Ar), 7.12–7.10 (m, 1H; Ar), 3.78 (s, 2H; 9*H*Flu), 2.39 ppm (s, 3H; CH_3); ^{13}C{^{1}H} NMR (125.77 MHz, [D$_6$]acetone): δ=144.4, 143.3, 143.3, 142.5, 135.5, 128.9, 128.4, 127.9, 127.9, 126.3, 121.2, 118.6, 36.6, 19.2 ppm.

2-(2,6-Dibromophenyl)-1,3-dioxane (11): 2,6-Dibromobenzaldehyde (**10**) (10.0 g, 37.9 mmol) was dissolved in dry CH_2Cl_2 (160 mL). Propanediol (6.4 mL, 88.5 mL), triethyl orthoformate (6.83 mL, 41 mmol), and anhydrous $ZrCl_4$ (1.0 g) were added at ambient temperature and stirred overnight. Then, NaOH (50 mL of a 10% solution) was added and stirred for an additional 1 h. The organic phase was separated and the aqueous phase was extracted with Et_2O (2×40 mL). The combined organic phases were washed with water (3×60 mL), dried over $MgSO_4$, and the volatiles were removed in vacuo to afford 12.0 g (98%) of **11** as a slightly yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.55 (d, ^3J=8.0 Hz, 2H; Ar), 7.00 (t, ^3J=8.0 Hz, 1H; Ar), 6.19 (s, 1H; C*H*), 4.33–4.29 (m, 2H; CH_2), 4.02–3.97 (m, 2H; CH_2), 2.44–2.34 (m, 1H; CH_2), 1.44–1.40 ppm (m, 1H, CH_2); ^{13}C{^{1}H} NMR (125.77 MHz, $CDCl_3$): δ=133.9, 132.5, 129.8, 122.9, 101.6, 66.7, 24.1 ppm.

2-Bromo-6-methylbenzaldehyde (12): Acetal **11** (10.1 g, 31.25 mmol) was dissolved in dry THF (200 mL). At −78°C *n*BuLi (15.1 mL, 2.5 M in hexane, 37.8 mmol) was added within 25 min, followed by 90 min additional stirring at that temperature. Then the reaction mixture was treated with methyliodide (5.99 g, 42.2 mmol) and stirred for 25 min at −78°C. Next, the reaction mixture was allowed to warm to ambient temperature within 1.5 h. The resulting solution was quenched with HCl (290 mL, 5 N) and stirred for 1.5 h at ambient temperature. The complete deprotection of the aldehyde was checked by GC analysis. Then the reaction mixture was subsequently extracted with diethyl ether (4×100 mL), the combined organic layers were washed with a 10% solution of sodium thiosulfate (100 mL), water (100 mL), dried over $MgSO_4$, filtered, and the volatiles were removed in vacuo. The resulting slightly yellow solid was purified by Kugelrohr distillation to afford **12** (5.97 g, 96%) as white crystals. R_f= 0.56 (cyclohexane/ethyl acetate 10:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ= 10.52 (s, 1H; C*H*O), 7.52–7.50 (m, 1H; Ar), 7.26 (t, ^3J=7.0 Hz, 1H; Ar), 7.22–7.20 (m, 2H; Ar), 2.58 ppm (s, 3H; CH_3); ^{13}C{^{1}H} NMR (125.77 MHz, $CDCl_3$): δ=194.6, 142.7, 133.6, 131.8, 131.7, 131.4, 128.3, 21.2 ppm.

3,3′,5′-Trimethylbiphenylcarbaldehyde (14): In a 250 mL Schlenk flask, dry dioxane (60 mL), $Pd(OAc)_2$ (175 mg), SIMES (*N*,*N*′-bis(2,4,6-trimethylphenyl)imidazolinium chloride, 777 mg), and Cs_2CO_3 (12.4 g) were stirred for 45 min at 80°C until a grey solution had formed. Benzaldehyde **12** (3.1 g, 15.6 mmol) and 3,5-dimethylphenylboronic acid (**13**) were added and the mixture was stirred for 2 h at 80°C (quantitative conversion, GC analysis). The reaction mixture was left to cool to ambient temperature and was then treated with NaOH (100 mL, 1 N) and diethyl ether (200 mL) and transferred into a separating funnel. The aqueous phase was extracted with Et_2O (2×100 mL) and the combined organic layers were subsequently washed with NaOH (100 mL, 1 N), brine (100 mL), dried over $MgSO_4$, and the volatiles were removed in vacuo. The resulting brown oil was purified by filtration over a short pad of silica gel (10×5 cm, eluent: cyclohexane/ethyl acetate 20:1) to afford **14** (3.1 g, 89%) as a yellow oil. R_f=0.66 (cyclohexane/ethyl acetate 10:1). The product was used without any further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ=9.96 (s, 1H; C*H*O), 7.44 (t, ^3J=7.8 Hz, 1H; Ar), 7.25 (d, ^3J=3.6 Hz, 2H; Ar), 7.04 (s, 1H; Ar), 6.95, (s, 2H; Ar), 2.65 (s, 3H; CH_3), 2.36 ppm (s, 6H; CH_3); ^{13}C{^{1}H} NMR (75.4 MHz, $CDCl_3$) δ= 195.0, 140.0, 139.0, 138.0, 132.7, 132.2, 131.9, 131.0, 129.7, 128.6, 128.2, 21.7, 21.4 ppm; IR (KBr): $\tilde{\nu}$=3436 (br), 2920, 2858, 2765, 1689, 1677, 1600, 1584, 1463, 1191 cm^{-1}.

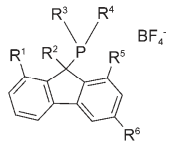
3,3′,5′-Trimethylbiphenylcarboxylic acid (15): Aldehyde **14** (2.75 g, 11.5 mmol) was dissolved in acetonitrile (18 mL, technical grade). NaH_2PO_4 (0.453 g, dissolved in 5.5 mL water) and H_2O_2 (1.93 mL of a 30% solution) were added. The reaction mixture was cooled to 0°C (ice/water) and $NaClO_2$ (2.2 g, dissolved in 19 mL water) was added within 60 min by a syringe. The solution was left to warm to ambient temperature and was stirred for an additional 3.5 h. Then Na_2SO_3 (100 mg) was added and the resulting reaction mixture was stirred for 5 min. After treatment with HCl (50 mL of a 10% solution), the reaction mixture was extracted with ether (3×75 mL). The combined organic phase was extracted with NaOH (4×75 mL, 1 N). The combined NaOH layers were acidified with HCl to pH 1 and extracted again with Et_2O. The combined organic layers were dried over $MgSO_4$ and the volatiles were removed in vacuo to afford **15** (2.95 g, quant.) as a colorless oil. The product was used without any further purification. ^{1}H NMR (300 MHz, $CDCl_3$): δ= 7.36–7.18 (m, 3H; Ar), 7.04 (s, 2H; Ar), 6.98 (s, 1H; Ar), 2.45 (s, 3H; CH_3), 2.32 ppm (s, 6H, CH_3); ^{13}C{^{1}H} NMR (75.4 MHz, $CDCl_3$): δ= 180.7, 140.6, 140.4, 138.0, 135.4, 132.1, 129.8, 129.4, 129.1, 127.6, 126.3, 21.4, 20.0 ppm.

1,3,8-Trimethylfluoren-9-one (16): In a 250 mL one-necked round-bottomed flask, the biphenylcarboxylic acid **15** (3.0 g, 12.9 mmol) was treated with concentrated sulphuric acid (40 mL) at 0°C (ice bath). The resulting dark-brown solution was stirred for 15 min at 0°C, then for additional 1 h at ambient temperature. After this time, the reaction mixture was poured onto ice (100 g) whereupon the color changed to a bright yellow. The suspension was neutralized with K_2CO_3 and extracted with Et_2O (3×100 mL). The combined organic phases were washed with brine (75 mL), dried over $MgSO_4$, filtered, and the volatiles removed in vacuo to afford **16** (2.8 g, 98%) as yellow crystals. R_f=0.52 (cyclohexane/ethyl acetate 10:1). The product was used without any further purification. ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.30–7.28 (m, 2H; Ar), 7.14 (s, 1H; Ar), 7.02–7.00 (m, 1H; Ar), 6.82 (s, 1H; Ar), 2.61 (s, 3H; CH_3), 2.57 (s, 3H; CH_3), 2.38 ppm (s, 3H; CH_3); ^{13}C{^{1}H} NMR (125.77 MHz, $CDCl_3$): δ= 196.3, 144.7, 144.5, 144.2, 138.9, 138.8, 133.4, 132.2, 131.7, 131.5, 128.8, 118.6, 117.4, 21.9, 17.7, 17.6 ppm; IR (KBr): ν=3049, 3020, 2919, 1698, 1615, 1595, 1454, 1373, 1296, 1170 cm^{-1}.

1,3,8-Trimethylfluorene (1c): 1,3,8-Trimethylfluoren-9-one (**16**) was reduced according to the general procedure of Carruthers et al.[8] 1,3,8-Trimethylfluoren-9-one (**16**) (2.74 g, 12.3 mmol) was dissolved in propionic acid (235 mL). Red phosphorus (3.0 g) and concentrated HI (40 mL) were added and the reaction mixture was refluxed for 24 h. Quantitative conversion was shown by TLC. The reaction mixture was diluted with water (250 mL), neutralized with NaOH, and extracted with Et_2O (4× 125 mL). The combined organic layers were washed with brine (2× 125 mL), dried over $MgSO_4$, filtered, and the volatiles were removed in vacuo to afford 2.56 g (quant.) of **1c** as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.60 (d, ^3J=7.5 Hz, 1H; Ar), 7.44 (s, 1H; Ar), 7.28 (t, ^3J=7.5 Hz, 1H; Ar), 7.10 (d, ^3J=7.0 Hz, 1H; Ar), 6.95 (s, 1H; Ar), 3.63 (s, 2H; CH_2), 2.44 (s, 3H; CH_3), 2.42 (s, 3H; CH_3), 2.40 ppm (s, 3H; CH_3); ^{13}C{^{1}H} NMR (125.77 MHz; $CDCl_3$): δ=141.3, 140.9, 140.8, 138.0, 135.6, 133.1, 132.8, 127.6, 126.4, 125.9, 117.1, 116.4, 33.4, 20.4, 17.9, 17.8 ppm; IR (KBr): $\tilde{\nu}$=3038, 3012, 2964, 2917, 2874, 1612, 1592, 1455, 1261 cm^{-1}.

9-Ethyl-2,7-dibromofluorene (19): In a 250 mL four-necked round-bottomed flask (wrapped with aluminum foil), 9-ethylfluorene (**2b**) (5 g, 25.7 mmol) was dissolved in dry $CHCl_3$ (50 mL). Anhydrous $FeCl_3$ (0.1 g, 0.63 mmol) was added. Under an argon atmosphere, bromine (8.64 g, 54.1 mmol, dissolved in 25 mL $CHCl_3$) was added dropwise at 0°C over 20 min while stirring. After completion of the addition, the reaction mixture was stirred for 3 h at ambient temperature. Then a solution of $Na_2S_2O_3$ (20% w/w in water) was added and the mixture was transferred to a separation funnel. The aqueous phase was discarded and the organic layer was subsequently washed with a solution of $NaHCO_3$ (saturated, 3×40 mL) and water (1×40 mL). The organic layer was dried over $MgSO_4$, filtered, and the volatiles were removed in vacuo to afford a yellow solid. Recrystallization from ethanol afforded **19** (6.3 g, 70%) as

Table 10. Fluorenyl phosphonium salts.



HBF_4 salt	R^1	R^2	R^3	R^4	R^5	R^6
17a	H	Me	Cy	Cy	H	H
17b	H	Me	*i*Pr	*i*Pr	H	H
17c	H	Et	Cy	Cy	H	H
17d	H	Et	*i*Pr	*i*Pr	H	H
17e	H	*i*Pr	Cy	Cy	H	H
17f	H	*i*Pr	*i*Pr	*i*Pr	H	H
17g	H	*n*Pr	Cy	Cy	H	H
17h	H	H	*t*Bu	*t*Bu	H	H
17i	H	$C_{18}H_{25}$	Cy	Cy	H	H
17j	H	$C_{18}H_{25}$	*i*Pr	*i*Pr	H	H
17k	H	Bn	Cy	Cy	H	H
17L	H	Bn	*i*Pr	*i*Pr	H	H
17m	H	Bn	*t*Bu	*n*Bu	H	H
17n	H	Et	*t*Bu	*n*Bu	H	H
17o	Me	Et	Cy	Cy	H	H
17p	Me	Et	Cy	Cy	Me	Me
17q	H	Ph	*i*Pr	*i*Pr	H	H

white crystals. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.61 (s, 2H; Ar), 7.56 (d, ^3J = 8.5 Hz, 2H; Ar), 7.48 (dd, ^3J = 8.5, ^4J = 1.5 Hz, 2H; Ar), 3.94 (t, ^3J = 5.0 Hz, 1H; 9*H*Flu), 2.06 (dq, ^3J = 5.5, 7.5 Hz, 2H; CH_2), 0.68 ppm (t, ^3J = 7.5 Hz, 3H; CH_3); ^{13}C{^{1}H} NMR (125.77 MHz, $CDCl_3$): δ = 148.9, 139.4, 130.3, 127.7, 121.2, 48.4, 25.3, 9.4 ppm; HRMS: *m/z*: calcd. for $C_{15}H_{12}Br_2$: 349.9305; found: 349.9286.

General procedure for the synthesis of fluorenyl phosphonium salts (Table 10): *n*BuLi (29 mmol, 2.5 M solution in hexane) was added to a solution of 9-substituted fluorene (31 mmol) in dry Et_2O (100 mL) at −60 °C. The solution immediately turned red and was stirred for 10 min at −60 °C, then for additional 2 h at ambient temperature. After cooling to −60 °C again, the dialkyl phosphonium chloride (22 mmol) was added. The reaction mixture was stirred for 10 min at −60 °C, then overnight at RT. After removing the LiCl by filtration over a short pad of Celite, the resulting clear filtrate was quenched with HBF_4 (31.5 mmol of a diethyl ether complex). After separation by means of suction filtration, the crude product was dissolved in $CHCl_3$ (20 mL) and added dropwise into Et_2O (1 L, vigorously stirred). Filtration and removal of the volatiles in vacuo afforded the pure product as a white solid.

MeFluPCy$_2$·HBF$_4$ (17a·HBF$_4$): 9-Methylfluorene (**2a**) (1.0 g, 5.55 mmol), *n*BuLi (2.7 mL of a 2.0 M in hexane, 5.4 mmol), Cy_2PCl (0.95 g, 4.08 mmol), HBF_4·Et_2O (1.4 mL, 5.55 mmol). **17a**·HBF_4 was isolated to give a white solid (1.35 g, 71 %). ^{1}H NMR (300 MHz, CD_3CN) δ = 8.02–7.99 (m, 2H; Ar), 7.81–7.78 (m, 2H; Ar), 7.66–7.61 (m, 2H; Ar), 7.56–7.50 (m, 2H; Ar), 6.00 (d, ^1J = 464 Hz, 1H; P*H*), 2.44–2.30 (m, 4H; CH_2), 2.03 (d, ^3J = 16.8 Hz, 3H; CH_3), 1.96–1.92 (m, 2H; *CH*), 1.75–1.49 (m, 8H; CH_2), 1.31–1.04 ppm (m, 8H; CH_2); ^{13}C{^{1}H} NMR (75.4 MHz, CD_3CN): δ = 140.9 (d, *J*(P,C) = 3.1 Hz), 140.1 (d, *J*(P,C) = 4.3 Hz), 130.0 (d, *J*(P,C) = 2.0 Hz), 128.6 (d, *J*(P,C) = 2.0 Hz), 124.6 (d, *J*(P,C) = 3.3 Hz), 121.3, 47.6 (d, *J*(P,C) = 33.9 Hz), 30.4 (d, *J*(P,C) = 35 Hz), 28.5 (d, *J*(P,C) = 3.9 Hz), 27.5 (d, *J*(P,C) = 3.8 Hz), 25.8 (d, *J*(P,C) = 13 Hz), 25.6 (d, *J*(P,C) = 13 Hz), 24.4, 21.6 ppm; ^{31}P{^{1}H} NMR (121.4 MHz, CD_3CN): δ = 38.8 ppm; ^{31}P NMR (121.4 MHz, CD_3CN): δ = 38.8 ppm (d, *J*(P,H) = 463 Hz).

MeFluP*i*Pr$_2$·HBF$_4$ (17b·HBF$_4$): 9-Methylfluorene (**2a**) (1.5 g, 8.31 mmol), *n*BuLi (4.05 mL, 2.0 M in hexane, 8.1 mmol), iPr_2PCl (0.9 mL, 5.67 mmol), HBF_4·Et_2O (2.4 mL, 9.51 mmol). Product **17b**·HBF_4 was isolated as a white solid (1.37 g, 63 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.94–7.86 (m, 4H; Ar), 7.60–7.49 (m, 4H; Ar), 7.27 (d, ^1J = 483 Hz, 1H; P*H*), 2.65–2.50 (m, 2H; *CH*), 2.15 (d, ^3J(P,H) = 16.8 Hz, 3H; CH_3), 1.33 (dd, ^3J = 7.2, ^3J(P,H) = 18.3 Hz, 6H; CH_3), 1.06 ppm (dd, ^3J = 7.5, ^3J(P,H) = 17.7 Hz, 6H; CH_3); ^{13}C{^{1}H} NMR (75.4 MHz, $CDCl_3$): δ = 142.2 (d, *J*(P,C) = 2.2 Hz), 140.2 (d, *J*(P,C) = 4.3 Hz), 130.3, 129.2 (d, *J*(P,C) = 1.7 Hz), 125.2 (d, *J*(P,C) = 3.7 Hz), 121.2, 47.9 (d, *J*(P,C) = 34 Hz), 22.7, 21.2 (d, *J*(P,C) = 36.3 Hz), 19.3 (d, *J*(P,C) = 2.9 Hz), 17.8 ppm (d, *J*(P,C) = 3.0 Hz); ^{31}P{^{1}H} NMR (121.4 MHz, $CDCl_3$): δ = 39.4 ppm; ^{31}P NMR (121.4 MHz, $CDCl_3$): δ = 39.4 ppm (d, *J*(P,H) = 482 Hz).

EtFluPCy$_2$·HBF$_4$ (17c·HBF$_4$): 9-Ethylfluorene (**2b**) (1.65 g, 8.55 mmol), *n*BuLi (3.3 mL, 2.5 M in hexane, 8.25 mmol), Cy_2PCl (1.26 g, 5.43 mmol), HBF_4·Et_2O (2.2 mL, 8.7 mmol). Product **17c**·HBF_4 was isolated as a white solid (1.97 g, 76 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.90–7.87 (m, 2H; Ar), 7.79 (d, ^3J = 7.9 Hz, 2H; Ar), 7.61–7.49 (m, 4H; Ar), 6.54 (d, ^1J = 480 Hz, 1H; P*H*), 2.80–2.71 (m, 2H; CH_2 (ethyl)), 2.30–2.18 (m, 2H; *CH*), 1.91–1.08 (m, 19H; CH_2), 0.32 ppm (t, ^3J = 6.9 Hz, 3H; CH_3); ^{13}C{^{1}H} NMR (75.4 MHz, $CDCl_3$) δ = 141.6 (d, *J*(P,C) = 4.5 Hz), 139.7 (d, *J*(P,C) = 3.0 Hz), 130.2, 129.1, 125.1 (d, *J*(P,C) = 3.0 Hz), 121.1, 52.9 (d, *J*(P,C) = 33 Hz), 31.2 (d, *J*(P,C) = 35 Hz), 29.4 (d, *J*(P,C) = 2.6 Hz), 28.0 (d, *J*(P,C) = 4 Hz), 27.4, 26.7 (d, *J*(P,C) = 13 Hz), 26.5 (d, *J*(P,C) = 13 Hz), 24.9, 6.7 ppm (d, *J*(P,C) = 11 Hz); ^{31}P{^{1}H} NMR (121.4 MHz, $CDCl_3$): δ = 34.4 ppm; ^{31}P NMR (121.4 MHz, $CDCl_3$): δ = 34.4 ppm (d, *J*(P,H) = 480 Hz).

EtFluP*i*Pr$_2$·HBF$_4$ (17d·HBF$_4$): 9-Ethylfluorene (**2b**) (0.54 g, 2.78 mmol), *n*BuLi (1.35 mL, 2.0 M in hexane, 2.7 mmol), iPr_2PCl (0.269 g, 1.76 mmol), HBF_4·Et_2O (0.55 mL, 2.7 mmol). Product **17d**·HBF_4 was isolated as a white solid (0.69 g, 99 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.90–7.82 (m, 4H; Ar), 7.61–7.50 (m, 4H; Ar), 6.70 (d, ^1J = 480 Hz, 1H; P*H*), 2.79–2.72 (m, 2H; CH_2 (ethyl)), 2.64–2.54 (m, 2H; *CH*), 1.30 (dd, ^3J = 7.2, ^3J(P,H) = 18.3 Hz, 6H; CH_3), 1.05 (dd, ^3J = 7.2, ^3J(P,H) = 17.4 Hz, 6H; CH_3), 0.33 ppm (t, ^3J = 6.9 Hz, 3H; CH_3); ^{13}C{^{1}H} NMR (75.4 MHz, $CDCl_3$): δ = 141.6 (d, *J*(P,C) = 4.8 Hz), 139.5 (d, *J*(P,C) = 3.0 Hz), 130.3 (d, *J*(P,C) = 2.1 Hz), 129.2 (d, *J*(P,C) = 3.4 Hz), 125.1 (d, *J*(P,C) = 3.4 Hz), 121.3, 52.7 (d, *J*(P,C) = 34 Hz), 27.6, 21.3 (d, *J*(P,C) = 36.7 Hz), 19.5 (d, *J*(P,C) = 2.4 Hz), 17.8 (d, *J*(P,C) = 3.5 Hz), 6.6 ppm (d, *J*(P,C) = 11 Hz); ^{31}P{^{1}H} NMR (121.4 MHz, $CDCl_3$): δ = 40.8 ppm; ^{31}P NMR (121.4 MHz, $CDCl_3$): δ = 40.8 ppm (d, *J*(P,H) = 478 Hz).

***i*PrFluPCy$_2$·HBF$_4$ (17e·HBF$_4$)**: 9-Isopropylfluorene (**2c**) (1.15 g, 5.54 mmol), *n*BuLi (2.7 mL, 2.0 M in hexane, 5.4 mmol), Cy_2PCl (0.9 mL, 4.08 mmol), HBF_4·Et_2O (1.2 mL, 4.76 mmol). Product **17e**·HBF_4 was isolated as a white solid (1.30 g, 64 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.89 (d, ^3J = 6.9 Hz, 2H; Ar), 7.79 (d, ^3J = 7.5 Hz, 2H; Ar), 7.62–7.50 (m, 4H; Ar), 6.79 (d, ^1J = 479 Hz, 1H; P*H*), 3.01 (dq, ^3J = 6.6, 4.8 Hz, 1H; *CH*CH_3), 2.21–2.09 (m, 2H; *CH*), 1.97–1.86 (m, 2H; CH_2), 1.81–1.59 (m, 6H; CH_2), 1.51–1.37 (m, 4H; CH_2), 1.23–1.07 (m, 8H; CH_2), 0.93 ppm (d, ^3J = 6.6 Hz, 6H; CH_3); ^{13}C{^{1}H} NMR (75.4 MHz, $CDCl_3$) δ = 141.5 (d, *J*(P,C) = 5.1 Hz), 139.6 (d, *J*(P,C) = *J* = 2.6 Hz), 130.3, 129.0, 125.7 (d, *J*(P,C) = 2.9 Hz), 121.1, 56.4 (d, *J*(P,C) = 33 Hz), 34.4, (d, *J*(P,C) = 35.6 Hz), 29.3 (d, *J*(P,C) = 3.8 Hz), 28.1 (d, *J*(P,C) = 3.7 Hz), 26.9 (d, *J*(P,C) = 12.9 Hz), 26.6 (d, *J*(P,C) = 12.5 Hz), 24.9, 17.8 ppm (d, *J*(P,C) = 6.6 Hz); ^{31}P{^{1}H} NMR (121.4 MHz, $CDCl_3$): δ = 25.0 ppm; ^{31}P NMR (121.4 MHz, $CDCl_3$): δ = 25.0 ppm (d, *J*(P,H) = 477 Hz).

***i*PrFluP*i*Pr$_2$·HBF$_4$ (17f·HBF$_4$)**: 9-Isopropylfluorene (**2c**) (1.16 g, 5.57 mmol), *n*BuLi (2.7 mL, 2.0 M in hexane, 5.4 mmol), iPr_2PCl (0.66 g, 4.1 mmol), HBF_4·Et_2O (1.2 mL, 4.76 mmol). Product **17f**·HBF_4 was isolated as a white solid (1.20 g, 71 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.90–7.82 (m, 4H; Ar), 7.62–7.50 (m, 4H; Ar), 6.99 (d, ^1J = 477 Hz, 1H; P*H*), 3.09–2.99 (m, 1H; *CH*), 2.59–2.44 (m, 2H; *CH*), 1.32 (dd, ^3J = 7.5, ^3J(P,H) = 18.9 Hz, 6H; CH_3), 1.03 (dd, ^3J = 7.5, ^3J(P,H) = 17.7 Hz, 6H; CH_3), 0.94 ppm (d, ^3J = 6.9 Hz, 6H; CH_3); ^{13}C{^{1}H} NMR (75.4 MHz, $CDCl_3$): δ = 141.5 (d, *J*(P,C) = 5.1 Hz), 139.4 (d, *J*(P,C) = 2.4 Hz), 130.3 (d, *J*(P,C) = 1.6 Hz), 129.1 (d, *J*(P,C) = 1.3 Hz), 125.7 (d, *J*(P,C) = 3.6 Hz), 121.2, 56.1 (d, *J*(P,C) = 33.2 Hz), 34.4, 21.1 (d, *J*(P,C) = 38.5 Hz), 19.5 (d, *J*(P,C) = 2.2 Hz), 17.8 (d, *J*(P,C) = 2.6 Hz), 6.6 ppm (d, *J*(P,C) = 6.5 Hz); ^{31}P{^{1}H} NMR (121.4 MHz, $CDCl_3$): δ = 31.3 ppm; ^{31}P NMR (121.4 MHz, $CDCl_3$): δ = 31.3 ppm (d, *J*(P,H) = 473 Hz).

***n*PrFluPCy$_2$·HBF$_4$ (17g·HBF$_4$)**: 9-*n*-Propylfluorene (**2d**) (3.0 g, 14.4 mmol), *n*BuLi (5.6 mL, 2.5 M in hexane, 14.0 mmol), Cy_2PCl (2.37 g, 10.2 mmol), HBF_4·Et_2O (2.0 mL, 14 mmol). Product **17g**·HBF_4 was isolat-

ed as a white solid (4.13 g, 73%). ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.87 (d, ^3J=7.5 Hz, 2H; Ar), 7.79 (d, ^3J=7.5 Hz, 2H; Ar), 7.59–7.50 (m, 4H; Ar), 6.54 (d, ^1J=480.5 Hz, 1H; P*H*), 2.67–2.63 (m, 2H; CH_2 (propyl)), 2.24–2.21 (m, 2H; C*H*), 1.91–1.10 (m, 19H; CH_2), 0.73 (t, ^3J=7.5 Hz, 3H; CH_3), 0.66–0.58 ppm (m, 2H; CH_2 (propyl)); ^{13}C{^{1}H} NMR (125.75 MHz, $CDCl_3$): δ=141.4 (d, J(P,C)=4.5 Hz), 140.2 (d, J(P,C)=3.8 Hz), 130.2, 129.1, 125.1 (d, J(P,C)=2.8 Hz), 121.1, 52.4 (d, J(P,C)=33 Hz), 40.0, 31.3 (d, J(P,C)=34.6 Hz), 29.4 (d, J(P,C)=3.6 Hz), 28.1 (d, J(P,C)=3.3 Hz), 26.8 (d, J(P,C)=13.8 Hz), 26.5 (d, J(P,C)=12.4 Hz), 24.9, 16.0 (d, J(P,C)=10.4 Hz), 13.6 ppm; ^{31}P{^{1}H} NMR (202.45 MHz, $CDCl_3$): δ=34.9 ppm; ^{31}P NMR (202.45 MHz, $CDCl_3$): δ=34.9 ppm (d, J(P,H)=483 Hz).

HFluP*t*Bu$_2$·HBF$_4$ (17h·HBF$_4$): Fluorene (**1a**) (0.505 g, 3.04 mmol) dissolved in dry THF (10 mL) was treated with *n*BuLi (1.5 mL, 2.0 M in hexane) at −80 °C. The mixture turned orange and was stirred for an additional 4 h at ambient temperature. Then *t*Bu$_2$PCl (0.476 g, 2.6 mmol) and dry heptane (10 mL) were added at −80 °C. The reaction mixture was refluxed overnight, filtered under Schlenk conditions over a short pad of Celite, and the clear filtrate was quenched with HBF$_4$·Et$_2$O (0.7 mL, 2.8 mmol) to afford a white residue, which could be crystallized from ethyl acetate. After separation of the solids by means of suction filtration, the crude product was dissolved in $CHCl_3$ (3 mL) and added dropwise into Et$_2$O (200 mL, vigorously stirred). Filtration and removal of the volatiles in vacuo afforded pure **17h**·HBF$_4$ (0.54 g, 52%) as a white solid. ^{1}H NMR (300 MHz, CD_3CN): δ=8.05–7.98 (m, 2H; Ar), 7.86–7.77 (m, 2H; Ar), 7.63–7.54 (m, 4H; Ar), 6.27 (d, ^1J=463 Hz, 1H; P*H*), 5.37 (d, ^2J(P,H)=15.6 Hz, 1H; C*H*), 1.85 (d, ^3J(P,H)=17.1 Hz, 9H; CH_3), 0.91 ppm (d, ^3J(P,H)=17.1 Hz, 9H; CH_3); ^{13}C{^{1}H} NMR (75.4 MHz, CD_3CN): δ=139.0, 135.1, 129.4 (d, J(P,C)=10 Hz), 128.1 (d, J(P,C)=32 Hz), 125.7 (d, J(P,C)=87 Hz), 121.2 (d, J(P,C)=28.0 Hz), 38.4 (d, J(P,C)=34 Hz), 36.5 (d, J(P,C)=23.7 Hz), 34.5 (d, J(P,C)=30.0 Hz), 27.5, 26.6 ppm; ^{31}P{^{1}H} NMR (121.4 MHz, CD_3CN): δ=52.1 ppm; ^{31}P NMR (121.4 MHz, CD_3CN): δ=52.1 ppm (d, J(P,H)=462 Hz).

C$_{18}$FluPCy$_2$·HBF$_4$ (17i·HBF$_4$): 9-Octadecylfluorene (**2e**) (2.48 g, 5.9 mmol), *n*BuLi (2.1 mL, 2.5 M in hexane, 5.25 mmol), Cy$_2$PCl (0.92 g, 3.94 mmol), HBF$_4$·Et$_2$O (1.8 mL). In the absence of precipitation, water (80 mL, treated with aqueous HBF$_4$ (8 N)) was added, whereupon a white solid precipitated. The solid was removed by means of suction filtration to afford **17i**·HBF$_4$ as a white solid (2.6 g, 94%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.87 (d, ^3J=7.2 Hz, 2H; Ar), 7.79–7.77 (m, 2H; Ar), 7.60–7.50 (m, 4H; Ar), 6.59 (d, ^1J=483 Hz, 1H; P*H*), 2.71–2.59 (m, 2H; CH_2), 2.27–2.13 (m, 2H; C*H*), 1.92–1.02 (m, 50H; CH_2), 0.87 (t, ^3J=6.6 Hz, 3H; CH_3), 0.60–0.49 ppm (m, 2H; CH_2); ^{13}C{^{1}H} NMR (75.4 MHz, $CDCl_3$): δ=141.4 (d, J(P,C)=4.2 Hz), 140.2, 130.2, 129.1, 125.1, 121.0, 52.4 (d, J(P,C)=32.2 Hz), 34.0, 31.9, 31.3 (d, J(P,C)=34.5 Hz), 29.7–29.1 (CH$_2$, 14×), 28.1 (d, J(P,C)=3.2 Hz), 26.8(d, J(P,C)=13.2 Hz), 26.6 (d, J(P,C)=12.6 Hz), 24.9, 22.7, 22.4 (d, J(P,C)=9.9 Hz), 14.1 ppm; ^{31}P{^{1}H} NMR (121.4 MHz, $CDCl_3$): δ=34.1 ppm; ^{31}P NMR (121.4 MHz, $CDCl_3$): δ=34.1 ppm (d, J(P,H)=482 Hz).

C$_{18}$FluP*i*Pr$_2$·HBF$_4$ (17j·HBF$_4$): 9-Octadecylfluorene (**2e**) (2.38 g, 5.7 mmol), *n*BuLi (2.0 mL, 2.5 M in hexane, 5.0 mmol), *i*Pr$_2$PCl (0.575 g, 3.77 mmol), HBF$_4$·Et$_2$O (2.0 mL, 9.8 mmol). In the absence of precipitation, the volatiles were evaporated in vacuo to give a colorless solid, which was dissolved in diethyl ether (50 mL) and treated with HBF$_4$·Et$_2$O (1 mL). Aqueous HBF$_4$ (50 mL, 4 N) was added, the mixture was stirred vigorously, and then the aqueous phase was separated and kept in an open beaker overnight. After this time, the crystals which had formed were separated by means of suction filtration and dried in vacuo to afford **17j**·HBF$_4$ (1.90 g, 81%) as white crystals. ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.88 (d, ^3J=6.9 Hz, 2H; Ar), 7.81 (d, ^3J=6.9 Hz, 2H; Ar), 7.59–7.53 (m, 4H; Ar), 6.65 (d, ^1J=481 Hz, 1H; P*H*), 2.71–2.61 (m, 2H; CH_2), 2.61–2.49 (m, 2H; C*H*), 1.31 (dd, ^3J=7.2, ^3J(P,H)=12.3 Hz, 6H; CH_3), 1.27–1.11 (m, 30H; CH_2), 1.05 (dd, ^3J=7.5, ^3J(P,H)=17.4 Hz, 6H; CH_3), 0.88 (t, ^3J=6.9 Hz, 3H; CH_3), 0.61–0.50 ppm (m, 2H; CH_2); ^{13}C{^{1}H} NMR (75.4 MHz, $CDCl_3$): δ=141.4 (d, J(P,C)=5.1 Hz), 139.9 (d, J(P,C)=2.9 Hz), 130.3, 129.2, 125.0 (d, J(P,C)=2.9 Hz), 121.3, 52.3 (d, J(P,C)=33.5 Hz), 34.1, 31.9, 29.6 (CH$_2$, 11×), 29.5, 29.4, 29.3, 29.1, 22.7, 22.2 (d, J(P,C)=10.5 Hz), 21.3 (d, J(P,C)=37 Hz), 19.5 (d, J(P,C)=1.8 Hz), 17.8 (d, J(P,C)=2.5 Hz), 14.1 ppm; ^{31}P{^{1}H} NMR (121.4 MHz, $CDCl_3$): δ=40.8 ppm; ^{31}P NMR (121.4 MHz, $CDCl_3$): δ=40.8 ppm (d, J(P,H)=480 Hz).

BnFluPCy$_2$·HBF$_4$ (17k·HBF$_4$): 9-Benzylfluorene (**2f**) (6.0 g, 23.2 mmol), *n*BuLi (8.6 mL, 2.5 M in hexane, 21.5 mmol), Cy$_2$PCl (3.85 g, 16.5 mmol), HBF$_4$·Et$_2$O (3.22 mL, 23.6 mmol). Product **17k**·HBF$_4$ was isolated as a white solid (5.43 g, 61%). ^{1}H NMR (500 MHz, [D$_6$]acetone): δ=8.32–8.30 (m, 2H; Ar), 7.88–7.86 (m, 2H; Ar), 7.60–7.57 (m, 4H; Ar), 6.90–6.87 (m, 1H; Ar), 6.82–6.79 (m, 2H; Ar), 6.70 (d, ^1J=472.5 Hz, 1H; P*H*), 6.69–6.67 (m, 2H; Ar), 4.25 (d, ^3J=7 Hz, 2H; CH_2), 2.88–2.79 (m, 2H; C*H*), 1.96–1.94 (m, 2H; CH_2), 1.77–1.08 ppm (m, 18H; CH_2); ^{13}C{^{1}H} NMR (125.77 MHz, [D$_6$]acetone): δ=142.7 ppm (d, J(P,C)=4.5 Hz), 140.5 (d, J(P,C)=3.5 Hz), 133.8, 133.7, 131.1, 129.3, 128.1, 127.7, 127.3 (d, J(P,C)=3.9 Hz), 122.1, 53.8 (d, J(P,C)=32.2 Hz), 39.5, 32.0 (d, J(P,C)=34.5 Hz), 30.0 (d, J(P,C)=3.5), 29.0 (d, J(P,C)=3.0), 27.2 (d, J(P,C)=12.0), 27.0 (d, J(P,C)=13.3), 25.6 ppm; ^{31}P{^{1}H} NMR (202.46 MHz, [D$_6$]acetone) δ=35.7 ppm; ^{31}P NMR (202.46 MHz, [D$_6$]acetone) δ=35.7 ppm (d, J(P,H)=472.6 Hz).

BnFluP*i*Pr$_2$·HBF$_4$ (17l·HBF$_4$): 9-Benzylfluorene (**2f**) (8.1 g, 31.3 mmol), *n*BuLi (11.6 mL, 2.5 M in hexane, 29 mmol), (*i*Pr)$_2$PCl (3.32 g, 22.3 mmol), HBF$_4$·Et$_2$O (4.35 mL, 31.9 mmol). After separation by means of suction filtration, the crude product was dissolved in acetonitrile (20 mL) and added dropwise into Et$_2$O (1 L, vigorous stirring). Filtration and removal of the volatiles in vacuo afforded the pure product **17l**·HBF$_4$ as a white solid (9.8 g, 95%). ^{1}H NMR (500 MHz, CD_3CN): δ=8.04–8.02 (m, 2H; Ar), 7.79–7.77 (m, 2H; Ar), 7.56–7.54 (m, 4H; Ar), 6.92–6.90 (m, 1H; Ar), 6.84–6.81 (m, 2H; Ar), 6.61–6.60 (m, 2H; Ar), 6.35 (d, ^1J=470 Hz, 1H; P*H*), 4.00 (d, ^3J=6.00 Hz, 2H; CH_2), 2.83–2.75 (m, 2H; C*H*), 1.18 (dd, ^3J=7.5, ^3J(P,H)=18.5 Hz, 6H; CH_3), 1.00 ppm (dd, ^3J=7.0, ^3J(P,H)=17.5 Hz, 6H; CH_3); ^{13}C{^{1}H} NMR (125.8 MHz, CD_3CN): δ=141.2 (d, J(P,C)=4.8 Hz), 138.7, 132.2 (d, J(P,C)=14.3 Hz), 130.0, 129.9, 128.2, 127.1, 126.7, 125.8 (d, J(P,C)=31.8 Hz), 38.5, 21.0 (d, J(P,C)=36.2 Hz), 18.3 (d, J(P,C)=2.3 Hz), 17.0 ppm (d, J(P,C)=1.4 Hz); ^{31}P{^{1}H} NMR (202.5 MHz, CD_3CN): δ=43.8 ppm; ^{31}P NMR (202.5 MHz, CD_3CN): δ=43.8 ppm (d, J(P,H)=465.2 Hz).

Synthesis of the fluorenyl phosphonium salts 17m and 17n

BnFluP(*n*Bu*t*Bu)·HBF$_4$ (17m·HBF$_4$): *n*BuLi (13.8 mL, 2.5 M in hexane, 34.7 mmol) was added to a solution of 9-benzylfluorene (**2f**) (9.24 g, 35.7 mmol) in dry THF (75 mL at −60 °C. The solution immediately turned red. After stirring for 1 h at ambient temperature, the reaction mixture was added to a solution of *t*BuPCl$_2$[109] (5.2 g, 32.7 mmol, dissolved in 50 mL dry Et$_2$O) at −80 °C. At the end of the addition, the red color remained. After stirring overnight at ambient temperature, *n*BuLi (16.8 mL, 2.5 M in hexane, 41.9 mmol) was added at −60 °C. The reaction mixture was stirred for 10 min at −60 °C, then for 2 h at ambient temperature. The suspension was filtered over a small pad of Celite and the clear reddish filtrate was quenched with HBF$_4$·Et$_2$O (4.0 mL, 29.3 mmol) to precipitate the phosphonium salt. After separation by means of suction filtration, the crude product was dissolved in acetonitrile (20 mL) and the solution was added dropwise to vigorously stirred Et$_2$O (1 L) to obtain a colorless precipitate. Filtration and removal of the volatiles in vacuo afforded **17m**·HBF$_4$ as a white solid (2.65 g, 17%). ^{1}H NMR (500 MHz, CD_3CN): δ=8.19–8.18 (m, 1H; Ar), 8.10–8.08 (m, 1H; Ar), 7.78–7.77 (m, 1H; Ar), 7.73–7.71 (m, 1H; Ar), 7.56–7.50 (m, 4H; Ar), 6.93–6.89 (m, 1H; Ar), 6.82–6.79 (m, 2H; Ar), 6.62–6.60 (m, 2H; Ar), 4.09–4.00 (m, 2H; CH_2, Bn), 2.81–2.77 (m, 1H; CH_2, *n*Bu), 2.42–2.38 (m, 1H; CH_2, *n*Bu), 1.95–1.94 (m, 2H; CH_2, *n*Bu), 1.66–1.59 (m, 2H; CH_2, *n*Bu), 1.01 (t, ^3J=7.6 Hz, 3H; CH_3, *n*Bu), 0.74 ppm (d, ^3J=17.5 Hz, 9H; CH_3, *t*Bu); ^{13}C{^{1}H} NMR (125.77 MHz, CD_3CN): δ=141.2 (d, J(P,C)=4.5 Hz), 141.0 (d, J(P,C)=4.4 Hz), 139.5 (d, J(P,C)=2.5 Hz), 138.4 (d, J(P,C)=1.9 Hz), 132.0 (d, J(P,C)=13.8), 132.1, 131.9, 130.0, 130.0, 129.8, 128.0 (d, J(P,C)=6.5 Hz), 127.0, 126.7, 126.4 (d, J(P,C)=3.4 Hz), 125.7 (d, J(P,C)=2.8 Hz), 121.1, 120.9, 52.1 (d, J(P,C)=32.8 Hz), 38.9, 33.5 (d, J(P,C)=34.0 Hz), 29.1 (d, J(P,C)=7.5 Hz), 25.2, 23.2 (d, J(P,C)=14.5 Hz), 14.5 (d, J(P,C)=37.7 Hz), 12.3 ppm; ^{31}P{^{1}H} NMR (202.5 MHz, CD_3CN): δ=39.8 ppm.

EtFluP(*n*Bu*t*Bu)·HBF$_4$ (17n·HBF$_4$): 9-Ethylfluorene (**2b**) (5.85 g, 30.0 mmol) was dissolved in dry THF (50 mL), treated with *n*BuLi

(11.5 mL, 2.5 M in hexane, 29.0 mmol) at −30 °C and stirred for 1 h at ambient temperature. Then tBuPCl$_2$[12] (4.36 g, 27.4 mmol) dissolved in dry THF (50 mL) was added at −80 °C to the red solution. The reaction mixture was stirred at ambient temperature for 14 h and the color turned slightly greenish. Completeness of the conversion was checked by ^{31}P NMR spectroscopy which showed one single signal at δ = 162.91 ppm (in benzene) for EtFluPtBuCl. At −30 °C, nBuLi (14.0 mL, 2.5 M in hexane, 35.0 mmol) was added and the reaction mixture stirred at ambient temperature overnight. The suspension was filtered over a small pad of Celite by using Schlenk technique. The clear reddish filtrate was treated with HBF$_4$·Et$_2$O (5.2 mL, 38 mmol). The volatiles were removed in vacuo to give a yellow residue, which was extracted with chloroform (6 mL), filtered, and the clear filtrate was added dropwise into Et$_2$O (200 mL, vigorously stirred) to precipitate the product. Filtration and removal of the volatiles in vacuo afforded **17n**·HBF$_4$ (5.3 g, 45 %) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.95 (d, ^3J = 6.5 Hz, 1H; Ar), 7.89–7.84 (m, 2H; Ar), 7.72 (d, ^3J = 8 Hz, 1H; Ar), 7.60–7.49 (m, 4H; Ar), 6.77 (d, ^1J = 481 Hz, 1H; P*H*), 2.81–2.73 (m, 1H; C*H*$_2$ (ethyl)), 2.69–2.61 (m, 1H; C*H*$_2$ (ethyl)), 2.42–2.32 (m, 1H; C*H*$_2$ (butyl)), 2.18–2.08 (m, 1H; C*H*$_2$ (butyl)), 1.88–1.77 (m, 2H; C*H*$_2$ (butyl)), 1.57–1.43 (m, 2H; C*H*$_2$ (butyl)), 0.97 (t, ^3J = 7.5 Hz, 3H; (butyl)), 0.85 (d, ^3J(P,H) = 17 Hz, 9H; C*H*$_3$), 0.32 ppm (t, ^3J = 7.5 Hz, 3H; (ethyl)); ^{13}C{^{1}H} NMR (125.75 MHz, $CDCl_3$): δ = 141.7 (d, J(P,C) = 4.4 Hz), 141.3 (d, J(P,C) = 4.5 Hz), 139.9, 139.0 (d, J(P,C) = 2.8 Hz), 130.4, 130.2, 129.3, 128.9, 125.9 (d, J(P,C) = 3.3 Hz), 124.7 (d, J(P,C) = 2.3 Hz), 121.4, 121.0, 52.2 (d, J(P,C) = 34 Hz), 33.7 (d, J(P,C) = 36.3 Hz), 28.8 (d, J(P,C) = 5.5 Hz), 28.1, 26.5, 24.1 (d, J(P,C) = 13.1 Hz), 15.0 (d, J(P,C) = 37.7 Hz), 13.2, 6.3 ppm (d, J(P,C) = 9.3 Hz); ^{31}P{^{1}H} NMR (202.45 MHz, $CDCl_3$): δ = 39.4 ppm; ^{31}P NMR (202.45 MHz, $CDCl_3$): δ = 39.4 ppm (d, J(P,H) = 480 Hz).

9-Et-1-MeFluPCy$_2$·HBF$_4$ (17o·HBF$_4$): 9-Ethyl-1-methylfluorene (**2g**) (2.0 g, 9.56 mmol), nBuLi (3.67 mL, 2.5 M in hexane, 9.18 mmol), Cy$_2$PCl (1.78 g, 7.65 mmol), HBF$_4$·Et$_2$O (1.25 mL, 9.18 mmol). Product **17o**·HBF$_4$ was isolated as a white solid (3.5 g, 93 %). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.86 (d, ^3J = 7.5 Hz, 1H, Ar), 7.74 (d, ^3J = 7.5 Hz, 1H, Ar), 7.68 (d, ^3J = 7.5 Hz, 1H; Ar), 7.59 (t, ^3J = 7.5 Hz, 1H; Ar), 7.54–7.47 (m, 2H; Ar), 7.24 (d, ^3J = 7.5 Hz, 1H; Ar), 6.50 (dd, ^1J = 465.5, ^3J = 4.0 Hz, 1H; P*H*), 3.06–2.97 (m, 1H; C*H*$_2$ (ethyl)), 2.79–2.68 (m, 2H; C*H*$_2$ (ethyl)+C*H* (Cy)), 2.66 (s, 3H; C*H*$_3$), 2.35–2.32 (m, 1H; C*H*(Cy)), 2.02–1.65 (m, 7H; C*H*$_2$), 1.56–1.34 (m, 7H; C*H*$_2$), 1.13–1.08 (m, 1H; C*H*$_2$), 0.91–0.87 (m, 4H; C*H*$_2$), 0.68–0.59 (m, 1H; C*H*$_2$), 0.39 ppm (t, ^3J = 7.0 Hz, 3H; C*H*$_3$); ^{13}C{^{1}H} NMR (125.75 MHz, $CDCl_3$): δ = 142.6 (d, J(P,C) = 4.0 Hz), 142.3 (d, J(P,C) = 4.5 Hz), 139.8 (d, J(P,C) = 4.5 Hz), 137.4 (d, J(P,C) = 3.3 Hz), 136.8 (d, J(P,C) = 2.8 Hz), 132.2, 131.0, 130.8, 129.2 (d, J(P,C) = 2.3 Hz), 124.6 (d, J(P,C) = 4.1 Hz), 121.4, 119.1, 54.7 (d, J(P,C) = 31.3 Hz), 32.1 (d, J(P,C) = 37.3 Hz), 31.8 (d, J(P,C) = 33.3 Hz), 30.6 (d, J(P,C) = 3.8 Hz), 28.7 (d, J(P,C) = 3.6 Hz), 28.5 (d, J(P,C) = 3.4 Hz), 27.2, 27.2, 27.2, 27.1, 27.1, 27.0, 26.9, 26.8, (d, J(P,C) = 13.2 Hz), 27.1 (d, J(P,C) = 13.2 Hz),25.2, 20.1, 7.4 ppm (d, J(P,C) = 11 Hz); ^{31}P{^{1}H} NMR (202.5 MHz, $CDCl_3$) δ = 27.5 ppm; ^{31}P NMR (202.5 MHz, $CDCl_3$): δ = 27.5 ppm (d, J(P,H) = 471 Hz).

9-Et-1,3,8-Me$_3$-FluPCy$_2$·HBF$_4$ (17p·HBF$_4$): 9-Ethyl-1,3,8-trimethylfluorene (**2h**) (0.8 g, 3.4 mmol), nBuLi (1.29 mL, 2.5 M in hexane), Cy$_2$PCl (0.633 g, 2.72 mmol), HBF$_4$·Et$_2$O (0.8 mL, 3.2 mmol). Product **17p**·HBF$_4$ was isolated as a white solid (1.29 g, 92 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.89 (d, ^3J = 7.5 Hz, 1H; Ar), 7.52 (s, 1H; Ar), 7.49–7.43 (m, 1H; Ar), 7.22 (d, ^3J = 7.5 Hz, 1H; Ar), 7.05 (s, 1H; Ar), 6.30 (dt, ^1J = 469, ^3J = 4.5 Hz, 1H; P*H*), 2.96 (dq, ^3J(P,H) = 5.7, 7.2 Hz, 2H; C*H*$_2$ (ethyl)), 2.66 (s, 3H; C*H*$_3$), 2.62 (s, 3H; C*H*$_3$), 2.44 (s, 3H; C*H*$_3$), 2.24–2.19 (m, 2H; C*H*), 2.12–1.04 (m, 20H; C*H*$_2$), 0.44 ppm (t, ^3J = 7.2 Hz, 3H; C*H*$_3$); ^{13}C{^{1}H} NMR (75.4 MHz, $CDCl_3$): δ = 142.6 (d, J(P,C) = 4.8 Hz), 142.5 (d, J(P,C) = 4.5 Hz), 140.8, 137.0 (d, J(P,C) = 4.4 Hz), 135.4 (d, J(P,C) = 3.2 Hz), 135.0 (d, J(P,C) = 3.2 Hz), 133.8 (d, J(P,C) = 4.1 Hz), 133.3 (d, J(P,C) = 2.3 Hz), 132.1 (d, J(P,C) = 2.3 Hz), 130.5 (d, J(P,C) = 2.4 Hz), 119.3, 118.6, 56.8 (d, J(P,C) = 28.9 Hz), 32.9 (d, J(P,C) = 17.3 Hz), 32.5 (d, J(P,C) = 17.7 Hz), 29.4 (d, J(P,C) = 3.3 Hz), 27.6 (d, J(P,C) = 4.8 Hz), 27.5 (d, J(P,C) = 4.8 Hz), 26.9 (d, J(P,C) = 13.5 Hz), 26.7 (d, J(P,C) = 13.1 Hz), 24.8, 23.7, 21.3, 20.3, 20.1, 7.1 ppm (d, J(P,C) = 11 Hz); ^{31}P{^{1}H} NMR (121.4 MHz, $CDCl_3$) δ = 27.7 ppm; ^{31}P NMR (121.4 MHz, $CDCl_3$): δ = 27.7 ppm (d, J(P,H) = 469 Hz).

PhFluPiPr$_2$·HBF$_4$ (17q·HBF$_4$): 9-Phenylfluorene (**5**) (0.72 g, 2.97 mmol), nBuLi (1.08 mL, 2.5 M solution in hexane), iPr$_2$PCl (0.33 mL, 2.03 mmol), HBF$_4$·Et$_2$O (0.6 mL, 2.37 mmol). Product **17q**·HBF$_4$ was isolated to give a white solid (0.84 g, 93 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.49 (d, ^1J = 490 Hz, 1H; P*H*), 7.98–7.91 (m, 4H; Ar), 7.85 (d, ^3J = 8.1 Hz, 2H; Ar), 7.64–7.52 (m, 4H; Ar), 7.45 (t, ^3J = 7.2 Hz, 2H; Ar), 7.37–7.32 (m, 1H; Ar), 2.30–2.21 (m, 2H; C*H*), 1.14 (dd, ^3J = 7.2, ^3J(P,H) = 18.0 Hz, 6H; C*H*$_3$), 1.02 ppm (dd, ^3J = 7.5, ^3J(P,H) = 17.7 Hz, 6H; C*H*$_3$); ^{13}C{^{1}H} NMR (75.4 MHz, $CDCl_3$): δ = 140.6 (d, J(P,C) = 4.5 Hz), 140.3 (d, J(P,C) = 2.9 Hz), 135.2, 130.5, 130.0, 129.4, 129.1, 127.3 (d, J(P,C) = 5.9 Hz), 126.7 (d, J(P,C) = 3.1 Hz), 121.5, 56.5 (d, J(P,C) = 33.8 Hz), 21.0 (d, J(P,C) = 37.3 Hz), 19.6 (d, J(P,C) = 2.4 Hz), 17.7 ppm (d, J(P,C) = 2.5 Hz); ^{31}P{^{1}H} NMR (121.4 MHz, $CDCl_3$): δ = 30.6 ppm; ^{31}P NMR (121.4 MHz, $CDCl_3$): δ = 30.6 ppm (d, J(P,H) = 489 Hz).

Synthesis of a monosulfonated 9-fluorenylphosphine, 9-Et-2-SO$_3$H-FluP-Cy$_2$·H$_2$SO$_4$ (18·H$_2$SO$_4$): Concentrated sulfuric acid (2.3 mL) was added to a solution of EtFluPCy$_2$·HBF$_4$ (**17c**·HBF$_4$) (2.35 g, 4.92 mmol) in dry CH_2Cl_2 (1 mL) at 0 °C. After stirring the solution at 40 °C overnight, ice was added (5 g). The reaction mixture was extracted with chloroform (3 × 10 mL). The combined organic layers were dried over MgSO$_4$. After filtration, the clear filtrate was reduced to a final volume of 5 mL in vacuo. The concentrate was added dropwise to diethyl ether (500 mL, vigorously stirred) to precipitate the product. Filtration and removal of the volatiles in vacuo afforded the pure product **18**·H$_2$SO$_4$ (1.8 g, 77 %) as a white solid. ^{1}H NMR (500 MHz, [D$_4$]methanol): δ = 8.22 (s, 1H; Ar), 8.10 (s, 2H; Ar), 8.09 (s, 1H; Ar), 7.86 (d, ^3J = 10 Hz, 1H; Ar), 7.68 (t, ^3J = 7.5 Hz, 1H; Ar), 7.60 (t, ^3J = 7.5 Hz, 1H; Ar), 2.87–2.81 (m, 1H; C*H*$_2$), 2.79–2.74 (m, 1H; C*H*$_2$), 2.69–2.61 (m, 1H; C*H*), 2.51–2.46 (m, 1H; C*H*), 2.05–1.05 (m, 20H; C*H*$_2$), 0.34 ppm (t, ^3J = 6.5 Hz, 3H; C*H*$_3$). ^{13}C{^{1}H} NMR (125.75 MHz, [D$_4$]methanol): δ = 147.5, 144.8 (d, J(P,C) = 4.8 Hz), 142.5 (d, J(P,C) = 4.5 Hz), 141.8 (d, J(P,C) = 2.9 Hz), 141.0 (d, J(P,C) = 2.0 Hz), 131.8, 130.6, 129.4, 126.4 (d, J(P,C) = 4.0 Hz), 124.0 (d, J(P,C) = 3.9 Hz), 123.2, 122.4, 53.9 (d, J(P,C) = 33.7 Hz), 32.4 (d, J(P,C) = 9.2 Hz), 32.1 (d, J(P,C) = 8.7 Hz), 30.8 (d, J(P,C) = 3.8 Hz), 30.4 (d, J(P,C) = 3.4 Hz), 29.6 (d, J(P,C) = 4.0 Hz), 29.5 (d, J(P,C) = 5.4 Hz), 28.9 (d, J(P,C) = 3.8 Hz), 28.5, 27.7 (d, J(P,C) = 4.9 Hz), 27.6 (d, J(P,C) = 4.3 Hz), 27.4 (d, J(P,C) = 11.3 Hz), 27.2 (d, J(P,C) = 11.9 Hz), 26.0 (d, J(P,C) = 2.8 Hz), 6.9 ppm (d, J(P,C) = 11.7 Hz); ^{31}P{^{1}H} NMR (202.46 MHz, [D$_4$]methanol): δ = 34.9 ppm; ESI-MS: positive ions **18**$^+$ (471.3), negative ions HSO_3 (97.3), BF_4 not observed. elemental analysis calcd for $C_{27}H_{37}O_7PS_2$ (568.7): C 57.02, H 6.56; found: C 56.93, H 7.26.

9-Et-2,7-dibromo-FluPiPr$_2$·HBF$_4$ (20·HBF$_4$): In a 100 mL Schlenk flask, diisopropylamine (1.03 mL, 7.4 mmol) was dissolved in dry THF (20 mL). At −60 °C, nBuLi (2.7 mL of a 2.0 M solution in hexane, 6.8 mmol) was added. The solution was stirred at −60 °C for 10 min, then for an additional 30 min at 0 °C. The formed LDA (LDA = lithium diisopropylamide) solution was added to a solution of 9-ethyl-2,7-dibromofluorene (**19**·HBF$_4$) (2.5 g, 7.08 mmol) in Et$_2$O (40 mL) at −60 °C. The red reaction mixture was stirred for 30 min at −60 °C, then for 1.5 h at ambient temperature (at lower temperatures a thick reddish precipitate was formed). Then iPr$_2$PCl (0.9 mL, 5.66 mmol) was added at −60 °C. The reaction mixture was stirred at ambient temperature for 2 h (color changed from red to yellow) and filtered over a small pad of Celite. The clear, slightly yellow filtrate was quenched with HBF$_4$·Et$_2$O (1.80 mL, 13.2 mmol) which led to precipitation of the phosphonium salt as a white solid. The solid was separated by means of suction filtration, slurried in water (15 mL, to remove residual ammonium salt) and filtered again. The collected white solid was dissolved in $CHCl_3$ (10 mL) and acetonitrile (1 mL), and the solution was added dropwise to vigorously stirred Et$_2$O (400 mL) to give a colorless precipitate. Filtration and removal of the volatiles in vacuo afforded **20**·HBF$_4$ as a white solid (2.82 g, 90 %). ^{1}H NMR (500 MHz, CD_3CN): δ = 7.98 (t, ^4J = 1.5 Hz, 2H; Ar), 7.91 (d, ^3J = 8.0 Hz, 2H; Ar), 7.81 (dt, ^3J = 8.0, ^4J = 1.5 Hz, 2H; Ar), 6.24 (d, ^1J = 470 Hz, 1H; P*H*), 2.80–2.71 (m, 2H; C*H*), 2.70–2.64 (m, 2H; C*H*$_2$), 1.17 (dd, ^3J = 7.5, ^3J(P,H) = 19 Hz, 6H; C*H*$_3$), 1.01 (dd, ^3J = 7.0, ^3J(P,H) = 18 Hz, 6H; C*H*$_3$), 0.30 ppm (t, ^3J = 7.0 Hz, 3H; C*H*$_3$); ^{13}C{^{1}H} NMR (125.75 MHz, CD_3CN): δ = 141.3 (d, J(P,C) = 2.1 Hz), 139.7 (d, J(P,C) = 4.5 Hz), 133.4, 127.9 (d, J(P,C) = 3.8 Hz), 123.1, 122.2 (d, J(P,C) = 2.0 Hz), 52.5 (d, J(P,C) = 33.9 Hz), 26.9, 20.9 (d, J(P,C) = 35.1 Hz), 18.3 (d, J(P,C) = 2.0 Hz), 16.9 (d,

$J(P,C) = 1.4$ Hz), 18.1 (d, $J(P,C) = 3.4$ Hz), 5.4 ppm (d, $J(P,C) = 10.1$ Hz); $^{31}P\{^1H\}$ NMR (202.45 MHz, CD_3CN): $\delta = 42.1$ ppm; ^{31}P NMR (202.45 MHz, CD_3CN): $\delta = 34.9$ ppm (d, $J(P,H) = 470.1$ Hz).

General procedures for the cross-coupling reactions: All cross-coupling reactions were carried out under an argon atmosphere in deaerated solvents (freeze and thaw).

Sonogashira reaction of aryl bromides (in diisopropylamine): Dry diisopropylamine (10 mL), aryl bromide (10 mmol), and acetylene (11 mmol) were placed in a Schlenk tube. Then the catalyst was added in the given concentration as a ready-made mixture[17] of $[Na_2PdCl_4]$/ligand (phosphonium salt)/CuI 4:8:3 under argon. Unless otherwise noted, the reaction mixture was stirred at 50°C in an aluminum block. After cooling to RT, the reaction mixture was diluted with diethyl ether (15 mL) and washed with water (10 mL), then the organic phase was dried over $MgSO_4$, filtered, and concentrated in vacuo. The product was isolated by column chromatography (silica gel, cyclohexane/ethyl acetate 100:2). Alternatively, the yield was either determined by GC analysis with hexadecane or diethylene glycol di-*n*-butyl ether as an internal standard or by determination of the mass of the isolated $iPr_2NH_2^+Br^-$.

Sonogashira reaction of aryl chlorides (in DMSO): Dry DMSO (5 mL, crown cap), aryl chloride (1.5 mmol), acetylene (2.1 mmol), and Na_2CO_3 (3 mmol) were placed in a Schlenk tube. Then the catalyst was added in the given concentration, $[Na_2PdCl_4]$/ligand (phosphonium salt)/CuI 4:8:3 under argon. The reaction mixture was stirred at 100–120°C in an aluminum block for 12 to 20 h. After cooling to RT, the reaction mixture was diluted with diethyl ether (15 mL) and washed with water (10 mL), then the organic phase was dried over $MgSO_4$, filtered, and concentrated in vacuo. The product was isolated by column chromatography (silica, cyclohexane/ethyl acetate 100:2. Alternatively, the yield was determined by GC analysis with hexadecane or diethylene glycol di-*n*-butyl ether as an internal standard.

Sonogashira reaction of aryl bromides (in water)

Preparation of the catalyst stock solution: $[Na_2PdCl_4]$ (0.05 mmol), 9-Et-2-SO_3HFlu-PCy_2-HSO_4 (**18**-H_2SO_4) (0.1 mmol) and Cs_2CO_3 (0.4 mmol) were placed in a Schlenk tube under argon. Degassed water (5.0 mL) was added and the mixture was stirred at 45°C for 2 h until the solution turned off white. The stock solution had a concentration of 1 mol% mL^{-1} mmol^{-1} aryl halide).

Cross-coupling reaction: Water (2 mL), isopropanol (2 mL), and the catalyst stock solution were added to the aryl bromide (1 mmol), acetylene (1.1 mmol), and Cs_2CO_3 (2 mmol) in a Schlenk tube. The reaction mixture was stirred at 100°C in an aluminum block for 1.5 to 4 h. After cooling to RT, the reaction mixture was diluted with diethyl ether (15 mL) and washed with water (10 mL), then the organic phase was dried over $MgSO_4$, filtered, and concentrated in vacuo. The product was isolated by column chromatography (silica gel, cyclohexane/ethyl acetate 100:2. Alternatively the yield was determined by means of GC analysis with hexadecane or diethylene glycol di-*n*-butyl ether as an internal standard.

Suzuki reaction of aryl halides (in dioxane)

Preparation of the catalyst stock solution: $[Na_2PdCl_4]$ (0.05 mmol), phosphonium salt (0.1 mmol), and Cs_2CO_3 (0.2 mmol) were placed in Schlenk tube. Dioxane (5.0 mL) was added and the mixture was stirred at 45°C for 2 h until the solution turned off white. This stock solution has a concentration of 1 mol% mL^{-1}·mmol aryl halide.

Cross-coupling reaction: Boronic acid (1.5 mmol), Cs_2CO_3 (2 mmol) in dioxane (5 mL), and the catalyst stock solution were added to the aryl halide (1 mmol). The reaction mixture was stirred at 100°C in an aluminum block. After cooling to RT, the reaction mixture was diluted with diethyl ether (15 mL) and washed with water (10 mL), then the organic phase was dried over $MgSO_4$, filtered, and concentrated in vacuo. The product was isolated by column chromatography (silica gel, cyclohexane/ethyl acetate 100:2). Alternatively, the yield was determined by GC analysis with hexadecane or diethylene glycol di-*n*-butyl ether as an internal standard.

Suzuki reaction of aryl halides (in water)

Preparation of the catalyst stock solution: The catalyst stock solution was prepared as described for the aqueous Sonogshira reaction; K_2CO_3 instead of Cs_2CO_3.

Cross-coupling reaction: Water (4 mL), the catalyst stock solution, and two drops of Labrasol were added to a mixture of aryl halide (1 mmol), boronic acid (1.2 mmol), and K_2CO_3 (3.2 mmol). The reaction mixture was stirred at the respective temperatures (see tables) for 0.5–20 h (see tables). After cooling to RT, the reaction mixture was diluted with diethyl ether (15 mL) and washed with water (10 mL). Then the organic phase was dried over $MgSO_4$, filtered, and concentrated in vacuo. The product was isolated by column chromatography (silica gel, cyclohexane/ethyl acetate 100:2). Alternatively, the yield was determined by GC analysis with hexadecane or diethylene glycol di-*n*-butyl ether as an internal standard.

Buchwald–Hartwig amination of aryl halides: Dry toluene (5 mL), aryl halide (5 mmol), amine (6 mmol), and NaO*t*Bu (6 mmol) were placed in a Schlenk tube. Next, the catalyst was added in the given concentration ($[Na_2PdCl_4]$/ligand phosphonium salt 1:2). The reaction mixture was stirred at 120°C in an aluminum block. After cooling to RT, the reaction mixture was diluted with diethyl ether (15 mL) and washed with water (10 mL). Then the organic phase was dried over $MgSO_4$, filtered, and concentrated in vacuo. The product was isolated by column chromatography (silica gel, cyclohexane/ethyl acetate 9:1). Alternatively, the yield was determined by GC analysis with hexadecane or diethylene glycol di-*n*-butyl ether as an internal standard.

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4.2. Synthese von Indenyl- und Cyclopentadienyldialkylphosphinen sowie Untersuchung deren katalytischer Aktivität

Der Inhalt dieses Kapitels wurde bereits veröffentlicht:

Christoph A. Fleckenstein, Herbert Plenio, "*1-Indenyldialkylphosphines and Cyclopentadienyldialkylphosphines as Ligands for High-Activity Palladium-Catalyzed Cross-Coupling Reactions with Aryl Chlorides*", *Organometallics*, **2007**, *26*, 10, 2758-2767.

In diesem Kapitel wird die Synthese und Evaluierung neuartiger, von den Fluorenylphosphinen abgeleiteter (Abb. 63) Indenyldialkyl- sowie Cyclopentadienyldialkylphosphine beschrieben.

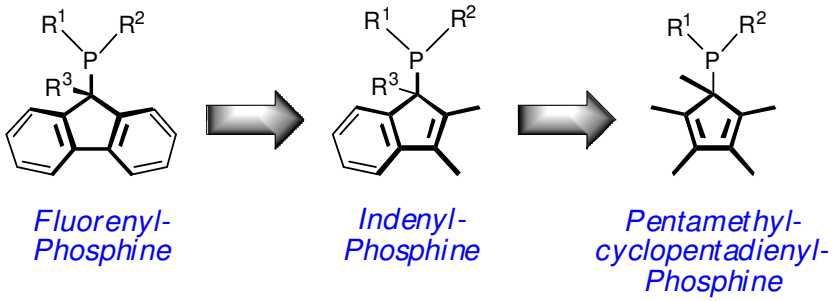

Abbildung 63. Von den Fluorenylphosphinen abgeleitet: Indenyl- und Pentamethylcyclopentadienylphosphine.

Die Synthese der jeweiligen Phosphine erfolgt analog derjenigen der Fluorenylphosphine durch Deprotonierung des entsprechenden Inden- oder Cyclopentadienprecursors mit *n*BuLi, Reaktion des Carbanions mit Dialkylphosphinchlorid und anschließender Protonierung des Phosphins zur Isolation als stabiles Phosphoniumsalz.

Auf diese Weise gelang die Darstellung von sechs Indenyldialkyl- sowie zwei Cyclopentadienyldialkylphosphinen unterschiedlichen sterischen und elektronischen Charakters.

Die neuen Phosphine wurden erfolgreich in Sonogashira-, Suzuki- und Buchwald-Hartwig-Kupplungen mit Arylchoriden eingesetzt.

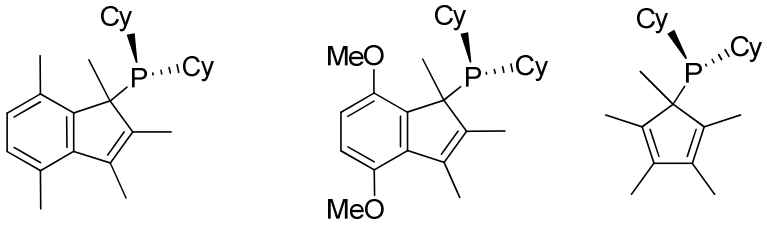

Abbildung 64. Hochaktive Indenyl- und Cp-Dialkylphosphine.*

Die elektronenreichsten und sterisch anspruchsvollsten Vertreter, in Abbildung 64 dargestellt, zeigten eine signifikant höhere Aktivität in Suzuki- und Buchwald-Hartwig-Reaktionen mit Arylchloriden als der Fluorenyl-Vergleichsligand EtFluPCy$_2$. Katalysatorbeladungen von 0.05-0.1 mol% für Suzuki- und 0.5-1 mol% für Buchwald-Hartwig-Reaktionen ermöglichten vollständigen Umsatz der Chloraromaten. Darüber hinaus konnte gezeigt werden, dass das gewählte Aminierungsprotokoll auch Aminoferrocen als Aminsubstrat toleriert. Eine derartige Arylierung von Aminoferrocen war bis dahin in der Literatur nicht bekannt.

In der Sonogashira-Reaktion konnte kein eindeutiger Trend bezüglich der Aktivität der neuen Liganden festgestellt werden. Mit wenigen Ausnahmen zeigten alle Palladium-Phosphin-Komplexe ähnliche Aktivitäten, die sich kaum von denen der Palladium-Fluorenylphosphin-Komplexe unterschieden. Aktivitätssteigerungen in der Sonogashira-Reaktion müssen also durch Änderung anderer Parameter erreichbar sein, unabhängig von den Phosphinliganden.

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1-Indenyldialkylphosphines and Cyclopentadienyldialkylphosphines as Ligands for High-Activity Palladium-Catalyzed Cross-Coupling Reactions with Aryl Chlorides

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The reactions of three deprotonated indenes (1,2,3-trimethyl, 1,2,3,4,7-pentamethyl, and 1,2,3-trimethyl-4,7-dimethoxy) and the lithium salt of pentamethylcyclopentadiene (Cp*) with $ClPR_2$ (R = *i*Pr, Cy) resulted in the formation of six indenylphosphines and two cyclopentadienylphosphines, isolated as the respective phosphonium salts. The Pd−phosphine complexes, formed in the presence of Na_2PdCl_4, base, and coupling partners, were shown to be highly active Pd complexes for various aryl chloride cross-coupling reactions. Quantitative yields in the Suzuki coupling are possible with 0.05−0.1 mol % of catalyst. Aryl chlorides can be coupled in quantitative yields in the Sonogashira reaction using 1 mol % of catalyst complex, while the Buchwald−Hartwig reaction typically requires 0.5 mol % of catalyst. In addition to the standard substrates, ferrocenylamine was subjected to Buchwald−Hartwig aminations, resulting in ferrocenylarylamines in near-quantitative yield.

Introduction

Trialkylphosphines with bulky substituents are highly useful ligands for catalytically active palladium complexes in various cross-coupling reactions of the Suzuki,[1−11] Sonogashira,[12−22] Heck,[23−28] Buchwald−Hartwig amination[29−35] and ether formation,[36] Negishi,[37] Stille,[38−40] Hiyama,[41] Kumada,[42] α-arylation,[43,44] and carbonylation types.[45] In particular, *t*Bu_3P has been used for a wide range of different coupling reactions, due to the high catalytic activity of its Pd complexes and its commercial availability.[46] *t*Bu_3P combines the two features which are said to be essential for trialkylphosphines for cross-coupling

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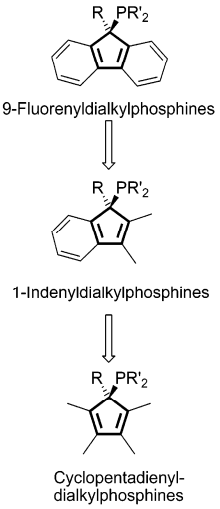
10.1021/om070094m CCC: $37.00
Publication on Web 04/11/2007

Chart 1. Relationship of Fluorenyl-, Indenyl-, and Cyclopentadienyldialkylphosphines

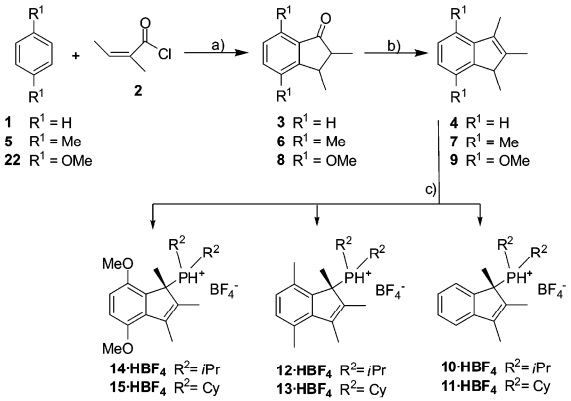


reactions: electron richness and steric bulk. We have recently reported a new class of 9-fluorenylphosphines[47] which combine the high catalytic activity of tBu$_3$P with the wide variability needed for the fine-tuning of the catalysts[48,49] or the introduction of phase tags[20,50−55] enabling biphasic catalysis[56] as well as catalyst recycling.[57,58]

Encouraged by the high catalytic activity and the facile synthesis of the fluorenyldialkylphosphines (isolated as the respective phosphonium salts), we wished to broaden this class of phosphines by variation of the fluorene lead structure. As visualized in Chart 1, the cyclopentadienyl ring embodies the core of the fluorenyl system. Replacement of the aromatic rings of fluorene by alkyl groups first leads to alkylated indenes and then to pentamethylcyclopentadiene (HCp*). All of these compounds are characterized by enhanced CH acidity of the central cyclopentadienyl ring, facilitating the selective formation of the respective carbanions. In this manner efficient C−C and C−P bond-forming reactions are possible. The respective phosphines stand a good chance to form a class of ligands with excellent properties in various Pd-mediated cross-coupling reactions.

Consequently, we wish to report here on the synthesis and characterization of various 1-indenyldialkylphosphonium and cyclopentadienyldialkylphosphonium salts and the application of the Pd complexes of the respective phosphines in Sonogashira, Suzuki, and Buchwald−Hartwig coupling reactions.

Scheme 1. Synthesis of Indenylphosphonium Salts[a]



[a] Reagents and conditions: (a) $AlCl_3$; (b) CH_3Li or CH_3MgI, H^+; (c) nBuLi, R_2PCl, Et_2O, −60 °C, HBF_4·Et_2O.

Results and Discussion

Synthesis of 1-Indenyldialkylphosphonium and Cyclopentadienyldialkylphosphonium Salts. Only a few cyclopentadienyl-[59−63] and indenyl-based trialkylphosphines[64−67] have been described in the literature, and none of them have been utilized in cross-coupling catalysis. In order to increase the steric bulk and to diversify the electronic nature of the such ligands, 1,2,3-trimethylindene (**4**), 1,2,3,4,7-pentamethylindene (**7**), and 4,7-dimethoxy-1,2,3-trimethylindene (**9**) were synthesized as backbones for phosphines. In general, the indenes were prepared via Friedel−Crafts acylation of the arene with tigloyl chloride (**2**) and subsequent ring closure, methylation, and acidic dehydration (Scheme 1). This synthetic strategy enables the easy modification of the 4,7-positions of indenes using the respective para-substituted arenes.

2,3-Dimethylindanone (**3**) was prepared according to the method of Rausch et al.[68] by reacting benzene (**1**) with $AlCl_3$ and tigloyl chloride (**2**) in benzene as a solvent in near-quantitative yield. When the same reaction protocol was utilized for the synthesis of 2,3,4,7-tetramethylindanone (**6**) with p-xylene (**5**) as reactant (and solvent), large amounts of isomerization products (32%) were formed due to a methyl shift of the aromatic methyl groups.[69,70] The separation of the two isomers was impractical on a multigram scale using rectification or column chromatography. It is noteworthy that even the improved synthesis of O'Hare et al.,[71,72] replacing the

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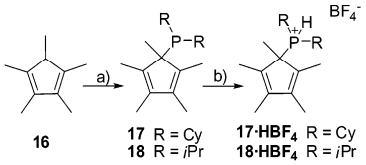
Scheme 2. Synthesis of Cyclopentadienylphosphonium Salts[a]



[a] Reagents and conditions: (a) *n*BuLi, R_2PCl, THF/Et_2O, −60 °C; (b) $HBF_4 \cdot Et_2O$.

undesirable CS_2 by dry CH_2Cl_2, could not completely suppress the isomerization (26% of the undesired isomer) in our hands. Consequently, for the synthesis of **6** we prefer CS_2, since the use of this solvent prevented the shift of methyl groups. ^1H NMR spectroscopy revealed that all indanones (**3**, **6**, **8**) were isolated as mixtures of the two cis/trans isomers in an approximate ratio of 3:1 for **3** and **6** and 4:1 for **8**. This poses no problem, since the cis/trans isomers react to give identical indenes. In order, to obtain the indenes **4**, **7**, and **9**, the respective indanones **3**, **6**, and **8** were reacted with MeLi or MeMgI to give the indanols, which were converted in situ into the desired indenes by acid-catalyzed elimination of water. As noted by O'Hare et al.,[72] the use of MeMgI as methylation agent gave better results than MeLi.

Deprotonation of the indenes **4**, **7**, and **9** with *n*BuLi and quenching with Cy_2PCl or iPr_2PCl gave the respective 1-indenylphosphines in good yields, which were isolated as the respective phosphonium salts. The Cp*-based phosphines were prepared in good yields (Scheme 2) by reactions of LiCp* with various chlorophosphines (iPr_2PCl, Cy_2PCl) and converted in situ into the respective phosphonium salts for easier storage and handling.[21,73] The free phosphines can be liberated from the phosphonium salts in quantitative yields by treatment with Et_3N (see the Experimental Section). The Cp* group provides steric bulk as well as an electron-rich environment.

Pd Complexes of 1-Indenyldialkylphosphines and Cyclopentadienyldialkylphosphines in the Suzuki Reaction. We first tested Pd complexes of the 1-indenyldialkylphosphines **10**−**15** and the Cp*-derived dialkylphosphines Cp*P*i*Pr$_2$ (**17**) and Cp*PCy_2 (**18**) for their reactivity in the Suzuki coupling (Table 1). As a reference phosphine, the recently reported highly active EtFluPCy_2[47] (**21**) was incorporated in the screening experiments. The reaction of *p*-chloroacetophenone with *p*-tolylboronic acid using 0.125 mol % Na_2PdCl_4 and 0.25 mol % phosphonium salt with Cs_2CO_3 in dioxane at 80 °C was initially used to probe the performance of the various phosphines. In general, complexes formed with phosphines bearing two Cy groups showed significantly better results than those with two *i*Pr groups. The top performers among the phosphines examined, Cp*PCy_2 (**17**), 1,2,3,4,7-Me_5IndPCy_2 (**13**), and 1,2,3-Me_3-4,7-$(MeO)_2$IndPCy_2 (**15**), showed nearly twice the high activity of EtFluPCy_2 (**21**), the best phosphine of the recently reported fluorenylphosphine family. In addition, 4,7-disubstituted 1-indenylphosphines and the cyclopentadienylphosphines show a better performance than phosphines based on the unsubstituted indene. Because of its high activity and its easy synthetic access, Cp*PCy_2 (**17**) was used as the ligand for further investigations.

As found by screening a wide range of different activated and deactivated aryl chlorides, 0.05 mol % of catalyst is sufficient to reach full conversion over 20 h; sterically hindered (entry 8) and electron-rich substrates (entry 2) require 0.1 mol % of catalyst to reach full conversion.

Pd Complexes of 1-Indenyl- and Cyclopentadienylphosphines in the Buchwald−Hartwig Reaction. In the present work we also examined the conversion of aryl chlorides as cheap and readily available starting materials with various aromatic and aliphatic amines. When the conditions recently reported by Beller et al. were applied without further optimization,[74] the screening of several indenyldialkylphosphines and cyclopentadienyldialkylphosphines in the reactions of 4-chlorotoluene with 3,5-dimethylaniline and 2,4-dimethylaniline revealed 1,2,3,4,7-pentamethylindenyldicyclohexylphosphine (**13**) to be the most active ligand for palladium (Table 2, entries 1 and 2). Typical catalyst loadings of 0.5 mol % Pd were applied at 120 °C using NaO*t*Bu as the base in toluene to give quantitative conversion. Some deactivated substrates required 1 mol % Pd to reach full conversion.

Activated and deactivated aryl chlorides were reacted with the respective amines (aniline, morpholine, α-methylbenzylamine, dibutylamine) under the same conditions in quantitative yields, whereas full conversion of deactivated aryl chlorides was only possible with difficulties applying the previously reported fluorenyldialkylphosphines.[47]

In addition to anilines, we also tested the coupling reactions of organometallic amines such as ferrocenylamine in Pd-catalyzed amination reactions for the first time—to the best of our knowledge. The resulting N-arylated aminoferrocenes have been rarely reported[75−78] and were said to be elusive.[79] Simple N-arylated aminoferrocenes such as ferrocenylphenylamine have been prepared by the reaction of ferrocenyl bromide with the sodium salt of an amide in the presence of copper(I) bromide/pyridine.[75] A recent synthetic strategy developed by Knochel et al.[79] requires a toxic tin reagent ($FcSnBu_3$), which is converted to FcMgBr and reacted with an arylazotosylate to obtain the aminated ferrocenyl derivative in 58% yield in the last reaction step. Utilizing Pd-catalyzed C−N coupling, ferrocenylarylamines can be synthesized in 85% yield in a single reaction step by employing the respective aryl chloride and ferrocenylamine, which is readily available using the improved synthesis of van Leusen and Hessen.[80] The amination of 3-chlorobenzyl trifluoride or 4-chloroanisole as a deactivated aryl chloride with ferrocenylamine using 0.5 mol % Pd and phosphine **13** gave the respective N-arylated aminoferrocenes (Table 2, entries 11 and 12). The redox potentials of the two ferrocenes (Table 2, entries 11 and 12) were determined by cyclic voltammetry and found to vary significantly depending on the nature of the para substituent (R = OMe, $E_{1/2}$ = 0.142 V; R = CF_3, $E_{1/2}$ = 0.268 V).

Pd Complexes of 1-Indenyl- and Cyclopentadienylphosphines in the Sonogashira Reaction. We initially tested the complexes of Pd with the various 1-indenyl- and Cp*-dialkylphosphines for their activity in the Sonogashira cross-coupling of phenylacetylene and 4-chloroanisole, applying the conditions described previously by us[47] (Table 3, entry 1). The top six of the eight phosphines screened show similar catalytic activities;

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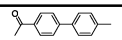
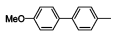
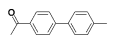
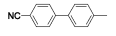
Table 1. Suzuki Reactions with Aryl Chlorides[a]

entry	aryl chloride	boronic acid	product	mol % catalyst / ligand	t (h)	conversion [c]
1				0.125 mol %/ **18**	15[d]	20 %
				0.125 mol %/ **17**	15[d]	60 %
				0.125 mol %/ **10**	15[d]	24 %
				0.125 mol %/ **11**	15[d]	36 %
				0.125 mol %/ **12**	15[d]	10 %
				0.125 mol %/ **13**	15[d]	51 %
				0.125 mol %/ **14**	15[d]	4 %
				0.125 mol %/ **15**	15[d]	49 %
				0.125 mol %/ **21**	15[d]	38 %
2				0.025 mol %/ **17**	20	11 %
				0.1 mol %/ **17**	20	≥ 99 %
3				0.025 mol %/ **17**	20	81 %
				0.05 mol %/ **17**	20	≥ 99 %
4				0.025 mol %/ **17**	20	85 %
				0.05 mol %/ **17**	20	≥ 99 %
5				0.025 mol %/ **17**	20	21 %
				0.1 mol %/ **17**	16	≥ 99 %
6				0.025 mol %/ **17**	20	63 %
				0.1 mol %/ **17**	16	≥ 99 %
7				0.1 mol %/ **17**	20	≥ 99 %
8				0.1 mol %/ **17**	16	≥ 99 %
9				0.05 mol %/ **17**	16	≥ 99 %

[a] Conditions: 1 mmol of aryl chloride, 1.5 mmol of boronic acid, 2.0 mmol of Cs_2CO_3, 5 mL of dioxane, 100 °C. The reaction conditions and the amount of catalyst have not been optimized. [b] Catalyst Na_2PdCl_4/ligand (1:2). [c] Average of two runs, determined by GC using hexadecane as internal standard. [d] Reaction was performed at 80 °C.

only **12** and **13**, which have methyl groups at the 4,7-positions of the indenyl ring, are less efficient. Interestingly, the same two phosphines did not behave conspicuously in Suzuki and amination reactions. A similar decrease in activity was also observed when Pd complexes of the related and recently reported fluorenyldialkylphosphines, bearing methyl moieties at the 1,8-positions, were used for Sonogashira reactions with aryl bromides.[47] With this in mind, it is quite surprising that phosphine ligands **14** and **15**, bearing a methoxy group instead of a methyl group at the 4,7-positions, show the highest catalytic activities within the range of the examined ligands. Steric effects within the phosphine ligand play a minor role in the Sonogashira reaction: phosphines bearing P*i*Pr$_2$ moieties at the phosphorus atom show activities comparable to those with a PCy$_2$ moiety. Because of its high activity, (4,7-dimethoxy-1,2,3-trimethylindenyl)dicyclohexylphosphine (**15**) was studied in more detail.

Sonogashira coupling of phenylacetylene with several aryl chlorides was tested (Table 2, entries 2−5). Excellent conversions of the reactants were observed for all substrates at 100−120 °C at 1 mol % of catalyst. More difficult acetylene substrates such as 1-hexyne were converted with activated as well as with deactivated aryl chlorides, giving conversions as high as 94%. Indenylphosphine- and cyclopentadienylphosphine-based palladium catalysts compare favorably with other catalytic systems described by us and by others for the conversion of aryl chlorides.[14,19,47,81−86]

There are several ligands of comparable (high) activity not different from those reported for other highly active phosphine ligands such as *t*Bu$_3$P and Ad$_2$PBn.[14] This indicates that the nature of the applied ligand is not limiting the catalytic activity of a Pd phosphine complex in the Sonogashira reaction with aryl chlorides. Further improvement of catalytic activity in Sonogashira reactions with aryl chlorides must go along with optimization of other factors such as reaction conditions and additives.

Summary and Conclusions

We were able to synthesize eight new 1-indenyldialkylphosphonium and cyclopentadienyldialkylphosphonium salts (alkyl = *i*Pr, Cy). The respective Pd complexes with the liberated phosphines are highly active for various cross-coupling reactions with aryl chlorides. Quantitative yields in Suzuki coupling screening for a wide range of different substrates were achieved with 0.05−0.1 mol % of catalyst. Aryl chlorides could be coupled in quantitative yields in the Sonogashira reaction using 1 mol % of catalyst and in the Buchwald−Hartwig reaction

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(85) Hierso, J.-C.; Fihri, A.; Amardeil, R.; Meunier, P.; Doucet, H.; Santelli, M.; Ivanov, V. V. *Org. Lett.* **2004**, *6*, 3473.
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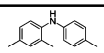
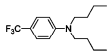
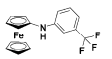
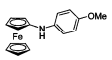
Table 2. Buchwald−Hartwig Amination[a] of Aryl Chlorides

entry	aryl chloride	amine	product	mol % catalyst / ligand	t (h)	conversion[b]
1				0.5 mol % / **18**	15	19 %
				0.5 mol % / **17**	15	40 %
				0.5 mol % / **10**	15	16 %
				0.5 mol % / **11**	15	16 %
				0.5 mol % / **12**	15	30 %
				0.5 mol % / **13**	15	63 %
				0.5 mol % / **14**	15	26 %
				0.5 mol % / **15**	15	43 %
				0.5 mol % / **21**	15	21 %
2				0.5 mol % / **17**	15	63 %
				0.5 mol % / **13**	15	54 %
				0.5 mol % / **15**	15	47 %
3				0.2 mol % / **13**	15	38 %
				0.5 mol % / **13**	20	≥ 99 %
4				0.5 mol % / **13**	15	51 %
				1.0 mol % / **13**	20	≥ 99 %
5				0.5 mol % / **13**	15	43 %
				1.0 mol % / **13**	20	95 %
6				0.5 mol % / **13**	15	≥ 99 %
7				0.5 mol % / **13**	15	≥ 99 %
8				0.5 mol % / **13**	15	≥ 99 %
9				0.5 mol % / **13**	20	≥ 99 %
10				0.5 mol % / **13**	20	16 %
11				0.5 mol % / **13**	20	85 %[c]
12				0.5 mol % / **13**	15	82 %[c]

[a] Conditions: 5 mL of toluene, 5 mmol of aryl chloride, 6 mmol of amine, 6 mmol of NaO*t*Bu, $Pd(OAc)_2$−ligand (phosphonium salt) (1:2), 120 °C. The reaction conditions have not been optimized. [b] Average of two runs, determined by GC using hexadecane as internal standard. [c] Isolated yield.

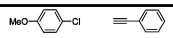
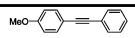
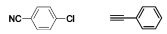
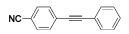
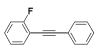
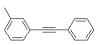
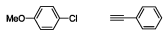
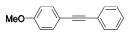
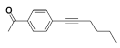
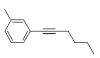
using 0.5 mol % of catalyst. Worthy of note is the successful implementation of ferrocenylamine in the Buchwald−Hartwig amination, resulting in ferrocenylarylamines in a single step in near-quantitative yield. In Sonogashira reactions the majority of the applied ligands showed activities comparable to reported activities of other highly active phosphine ligands such as tBu$_3$P and Ad$_2$PBn.[14] Further improvement of catalytic activity in Sonogashira reactions with aryl chlorides must go along with optimization of other factors such as reaction conditions and additives. Cp*PCy$_2$ (**17**) and 1,2,3,4,7-Me$_5$IndPCy$_2$ (**13**) are favorable ligands for amination reactions; Cp*PCy$_2$ (**17**) is favorable for Suzuki reactions involving aryl chlorides. Worthy of note is the facile synthesis of Cp*PCy$_2$ in a single step from commercially available precursors and the remarkable catalytic activity of the respective Pd complexes.

Experimental Section

All chemicals were purchased as reagent grade from commercial suppliers and used without furher purification, unless otherwise noted. Methyllithium (3.0 M in dimethoxyethane) was purchased from Sigma-Aldrich. THF was distilled over potassium and benzophenone under an argon atmosphere, diethyl ether was distilled over sodium/potassium alloy and benzophenone under an argon atmosphere, and toluene was distilled over sodium and benzophenone under an argon atmosphere. Dioxane was dried over CaH_2. Proton (^{1}H NMR), carbon (^{13}C NMR), and phosphorus (^{31}P NMR) nuclear magnetic resonance spectra were recorded on a Bruker DRX 500 spectrometer at 500, 125.75 and 202.46 MHz, respectively, or on a Bruker DRX 300 spectrometer at 300 and 75.07 MHz at 293 K. The chemical shifts are given in parts per million (ppm) on the delta scale (δ) and are referenced to tetramethylsilane (δ 0 ppm) for ^{1}H NMR and 65% aqueous H_3PO_4 (δ 0 ppm) for ^{31}P NMR. Abbreviations for NMR data: s = singlet; d = doublet; t = triplet; q = quartet; qi = quintet; dd = doublet of doublets; dt = doublet of triplets; dq = doublet of quartets; tt = triplet of triplets; m = multiplet. Mass spectra were recorded on a Finnigan MAT 95 magnetic sector spectrometer. Thin-layer chromatography (TLC) was performed using Fluka silica gel 60 F 254 (0.2 mm) on aluminum plates. Silica gel columns for chromatography were prepared with E. Merck silica gel 60 (0.063−0.20 mesh ASTM).

Cyclic voltammetry was carried out with an EG&G 263A-2 potentiostat. Cyclic voltammograms were recorded in dry CH_2Cl_2 under an argon atmosphere at ambient temperature. A three-electrode configuration was employed. The working electrode was a Pt disk (diameter 1 mm) sealed in soft glass with a Pt wire as counter electrode. The pseudo reference electrode was an Ag wire. Potentials were calibrated internally against the formal potential

Table 3. Sonogashira Reactions with Aryl Chlorides[a]

entry	aryl chloride	acetylene	product	mol % catalyst / ligand	t (h) / T (°C)	conversion [b]
1				1 mol %/ **18**	20 / 110	37 %
				1 mol %/ **17**	20 / 110	35 %
				1 mol %/ **10**	20 / 110	44 %
				1 mol %/ **11**	20 / 110	41 %
				1 mol %/ **12**	20 / 110	8 %
				1 mol %/ **13**	20 / 110	12 %
				1 mol %/ **14**	20 / 110	45 %
				1 mol %/ **15**	20 / 110	51 %
				1 mol %/ **21**	20 / 110	52 %
2				1 mol %/ **15**	15 / 100	95 %
3				1 mol %/ **15**	15 / 100	43 %
				1 mol %/ **15**	15 / 120	96 %
4				1 mol %/ **15**	15 / 120	91 %
5				1 mol %/ **15**	15 / 120	83 %
6				1 mol %/ **15**	15 / 120	94 %
7				1 mol %/ **15**	15 / 120	80 %

[a] Conditions: 1.5 mmol of aryl chloride, 2.1 mmol of acetylene, 3 mmol of Na_2CO_3, 5 mL of DMSO, catalyst 1 mol % (Na_2PdCl_4−ligand−CuI (4:8:3)). [b] Average of two runs.

of ferrocene (460 mV (CH_2Cl_2) vs Ag/AgCl).[87] NBu_4PF_6 (0.1 mol/L) was used as the supporting electrolyte.

GC experiments were run on a Clarus 500 GC instrument with autosampler and FID detector: column, Varian CP-Sil 8 CB (l = 15 m, d_i = 0.25 mm, d_F = 1.0 μm); N_2 flow (17 cm/s (split 1:50)); injector temperature, 270 °C; detector temperature, 350 °C; temperature program, isotherm 150 °C for 5 min, heating to 300 °C at a rate of 25 °C/min, isotherm for 15 min. HCp* was synthesized according to the Kohl and Jutzi procedure.[88] 2,3-Dimethyl-1-indanone (**3**) and 1,2,3-trimethylindene (**4**) were prepared according to the method of Rausch et al.[68] The ^{1}H NMR spectra were identical with those in the literature for **3**[89] and for **4**.[68]

2,3,4,7-Tetramethyl-1-indanone (6).[72] Under an argon atmosphere $AlCl_3$ (64 g, 0.48 mol) and CS_2 (250 mL) were placed in a 1 L three-necked round-bottomed flask fitted with a magnetic stirrer, addition funnel, thermometer, and reflux condenser. A mixture of tigloyl chloride (**2**; 42 g, 0.35 mol) and *p*-xylene (**5**; 42.8 mL, 0.35 mol) was added over a period of 1 h at −10 °C with vigorous stirring. The reaction mixture was stirred for 2 h at that temperature and then warmed to ambient temperature and stirred overnight. The brown reaction mixture was then refluxed for 3 h, cooled to ambient temperature, and poured carefully onto a mixture of concentrated HCl (300 mL) and ice (500 g). The CS_2 layer was separated in a separation funnel, and the aqueous layer was extracted with diethyl ether (3 × 100 mL). The combined organic layers were dried over magnesium sulfate and filtered, and the volatiles were removed in a rotary evaporator to give a red-brown liquid. This residue was rectified using a 35 cm Vigreux column to afford 2,3,4,7-tetramethyl-1-indanone (**6**; 34 g, 52%, 95−100 °C, 1.5−1.2 mbar) as a pale yellow liquid. **6** was found to be a mixture of the two isomers of 2,3,4,7-tetramethyl-1-indanone (the ratio of **6a** to **6b** was approximately 3:1). The ^{1}H NMR spectrum was identical with that in the literature.[71,72,90]

1,2,3,4,7-Pentamethylindene (7). In a 1 L three-necked round-bottomed flask fitted with a magnetic stirrer and a reflux condenser, 2,3,4,7-tetramethyl-1-indanone (**6**; 19.52 g, 0.1 mol) was dissolved in dry diethyl ether (300 mL) under an argon atmosphere. The mixture was cooled with an ice bath; methyllithium (45 mL, 3.0 M solution in dimethoxyethane, 0.135 mol) was added dropwise via a syringe. The mixture was refluxed for 3 h. The yellow reaction mixture was cooled to ambient temperature, and a mixture of concentrated HCl (20 mL) and H_2O (60 mL) was added via an addition funnel. The resulting mixture was transferred to a separation funnel and extracted with diethyl ether (3 × 200 mL). The combined organic layers were stirred overnight with 15 mL of concentrated HCl. After this time the reaction mixture was carefully adjusted to pH 7 with a saturated aqueous solution of Na_2CO_3. The reaction mixture was transferred into a separation funnel. The organic layer was washed with H_2O (3 × 100 mL), dried over $MgSO_4$, and filtered, and the volatiles were removed under reduced pressure to give a yellow liquid. This residue was purified via column chromatography (SiO_2, 25 × 9 cm; eluent cyclohexane) to afford 1,2,3,4,7-pentamethylindene (**7**; 8.35 g, 44%) as a yellow liquid followed by **6** (starting material; 9.60 g, 49%) (eluent cyclohexane−ethyl acetate (10:1)) as a yellow liquid. The NMR spectra were identical with those reported in the literature.[72]

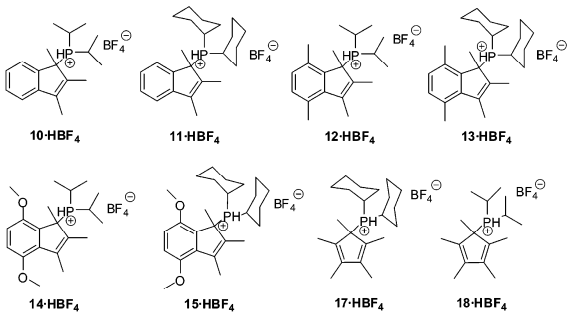
4,7-Dimethoxy-2,3-dimethyl-1-indanone (8). $AlCl_3$ (64 g, 0.48 mol) and CH_2Cl_2 (250 mL) (dried over $MgSO_4$) were placed under an argon atmosphere in a 500 mL three-necked round-bottomed flask fitted with a magnetic stirrer, addition funnel, inner thermometer, and reflux condenser. A mixture of tigloyl chloride (**2**; 42 g, 0.35 mol) and 1,4-dimethoxybenzene (**22**; 48.4 g, 0.35 mol, dissolved in 75 mL of CH_2Cl_2) was added over a period of 1 h at −10 °C with vigorous stirring. After 2 h of stirring at −2 to −5 °C, the mixture was warmed to ambient temperature and was

(87) Connelly, N. G.; Geiger, W. E. *Chem. Rev.* **1996**, *96*, 877.
(88) Kohl, F. X.; Jutzi, P. *Organomet. Synth.* **1986**, *3*, 489.
(89) Sarrazin, J.; Tallec, A. *Tetrahedron Lett.* **1977**, *18*, 1579.
(90) Kaminsky, W.; Rabe, O.; Schauwienold, A.-M.; Schupfner, G. U.; Hanss, J.; Kopf, J. *J. Organomet. Chem.* **1995**, *497*, 181.

stirred overnight. The dark red mixture was then refluxed for 2 h; after it was cooled to ambient temperature, the reaction mixture was poured carefully onto a mixture of concentrated HCl (300 mL) and ice (500 g). Then the resulting yellow mixture was transferred to a separation funnel, the lower (CH_2Cl_2) layer was isolated, and the aqueous layer was extracted with diethyl ether (3 × 100 mL). The combined organic layers were dried over magnesium sulfate and filtered, and the volatiles were removed under reduced pressure to give a dark brown liquid. This residue was distilled using a 15 cm Vigreux column to give an orange-yellow light viscous liquid (110−115 °C, 0.8 mbar). The liquid was purified via column chromatography (SiO_2, 25 × 9 cm; eluent cyclohexane−ethyl acetate (1:1)) to afford 2,3-dimethyl-4,7-dimethoxy-1-indanone (**8**; 9.53 g, 12%), R_f = 0.35 (cyclohexane−ethyl acetate (5:1)) as a yellow solid. **8** was found to be a mixture of the two isomers of 4,7-dimethoxy-2,3-dimethyl-1-indanone (the ratio of **8a** to **8b** was approximately 4:1). ^{1}H NMR (500 MHz, $CDCl_3$): **8a**, δ 7.01 (d, ^3J = 8.0 Hz, 1H, arom), 6.74 (d, ^3J = 8.5 Hz, 1H, arom), 3.89 (s, 3H, O−CH_3), 3.84 (s, 3H, O−CH_3), 2.97 (qd, ^3J = 7.0 Hz, ^3J = 3.0 Hz, 1H, C*H* position 2), 2.22 (qd, ^3J = 7.5 Hz, ^3J = 3.0 Hz, 1H, C*H* position 3), 1.40 (d, ^3J = 7.0 Hz, 3H, CHCH_3), 1.26 (d, ^3J = 7.5 Hz, 3H, CHCH_3); **8b**, δ 6.99 (d, ^3J = 9.0 Hz, 1H, arom), 6.72 (d, ^3J = 7.5 Hz, 1H, arom), 3.89 (s, 3H, O−CH_3), 3.86 (s, 3H, O−CH_3), 3.53 (qi, ^3J = 7.5 Hz, 1H, C*H* position 2), 2.74 (qi, ^3J = 7.5 Hz, 1H, C*H* position 3), 1.20 (d, ^3J = 7.0 Hz, 3H, CHCH_3 position 2) 1.16 (d, ^3J = 7.0 Hz, 3H, CHCH_3 position 3). ^{13}C{^{1}H} NMR (125.77 MHz, $CDCl_3$): **8a**, δ 207.2, 151.8, 150.9, 148.2, 124.8, 117.5, 109.8, 56.0, 55.8, 51.6, 39.8, 19.5, 16.2; **8b**, δ 206.5, 151.5, 150.3, 149.3, 124.8, 116.9, 109.7, 56.0, 55.8, 47.1, 34.5, 16.1, 14.2. HRMS (*m/z*): calcd for $C_{13}H_{16}O_3$, 220.1099; found, 220.10909.

4,7-Dimethoxy-1,2,3-trimethylindene (9). Diethyl ether (100 mL) and Mg turnings (0.96 g, 39 mmol) were placed in a 250 mL three-necked round-bottomed flask fitted with a magnetic stirrer and reflux condenser. Under an argon atmosphere a solution of CH_3I (2.66 mL, 43 mmol) in degassed and dried diethyl ether (50 mL) was added via an addition funnel. The resulting gray solution was stirred for 45 min before addition of dry light petroleum (bp 80−110 °C; 20 mL). The ether was then removed under reduced pressure to yield a gray suspension which was cooled with ice. A solution of 2,3-dimethyl-4,7-dimethoxy-1-indanone (**8**; 7 g, 32 mmol) in pentane (50 mL) was added dropwise over a period of 40 min; then the mixture was refluxed for 3 h. At this point the yellow reaction mixture was cooled to 0 °C and a mixture of HCl (10 mL) and H_2O (40 mL) was added via an addition funnel. The resulting solution was transferred into a separation funnel and extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with 0.25 M aqueous sodium thiosulfate (3 × 30 mL) and filtered into a round-bottomed flask. Concentrated HCl (15 mL) was added, and the mixture was stirred at ambient temperature overnight. Then pH 7 was adjusted by addition of a saturated aqueous solution of Na_2CO_3. The organic layer was washed with water (3 × 100 mL), dried over $MgSO_4$, and filtered, and the volatiles were removed in vacuo. The residual liquid was purified via column chromatography (SiO_2, 35 × 9 cm; initial eluent cyclohexane−ethyl acetate (50:1)) to afford two fractions: 1,2,3-trimethyl-4,7-dimethoxyindene (**9**; 4.63 g, 66%) as a yellow liquid with R_f = 0.42 (eluent cyclohexane−ethyl acetate (2:1)) and 4,7-dimethoxy-2,3-dimethyl-1-indanone (**8**; starting material) with R_f = 0.35 (cyclohexane−ethyl acetate (5:1)) as a pale yellow liquid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.70 (d, ^3J = 8.5 Hz, 1H, arom), 6.56 (d, ^3J = 9 Hz, 1H, arom), 3.81 (s, 3H, O−CH_3), 3.78 (s, 3H, O−CH_3), 3.23 (q, ^3J = 7.5 Hz, 1H, C*H*), 2.17 (m, 3H, CH_3), 1.90 (m, 3H, CH_3), 1.28 (d, ^3J = 7.0 Hz, 3H, CHCH_3). ^{13}C{^{1}H} NMR (125.77 MHz, $CDCl_3$): δ 150.6, 149.1, 142.9, 137.2, 135.7, 131.1, 111.1, 107.5, 56.7, 56.0, 46.4, 14.7, 13.4, 12.0. HRMS (*m/z*): calcd for $C_{14}H_{18}O_2$, 218.1306; found, 218.13110.

Chart 2. Indenyl- and Cyclopentadienyldialkylphosphonium Salts



Diagrams of the indenyl− and Cp*−dialkylphosphonium salts are given in Chart 2.

(1,2,3-Tetramethylindenyl)diisopropylphosphonium Tetrafluoroborate (10·HBF$_4$). In a 250 mL Schlenk flask 1,2,3-trimethylindene (**4**; 5.14 g, 32.5 mmol) was dissolved in Et_2O (100 mL) under an argon atmosphere. The mixture was cooled to −60 °C (N_2/isopropyl alcohol), and *n*BuLi (12.38 mL, 2.5 M solution in hexane, 31 mmol) was added. The solution was stirred for 10 min at −60 °C and then for 3 h at ambient temperature. A white precipitate was formed. Then the mixture was cooled to −60 °C and *i*Pr_2PCl (4.1 mL, 25.8 mmol) was added. The mixture was warmed to room temperature and stirred for an additional 2 h, and the LiCl that formed was removed by filtration over a pad of Celite under Schlenk conditions. The resulting slightly yellowish filtrate was treated dropwise with HBF_4·Et_2O (4.42 mL, 32 mmol) to give a white precipitate, which was separated via filtration and dissolved in 10 mL of acetonitrile. After filtration the clear filtrate was dropped into Et_2O (900 mL, vigorously stirred). The white precipitate that formed was separated via suction filtration. Removal of the volatiles in vacuo afforded **10·HBF$_4$** as a white solid (8.53 g, 91%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.68 (d, ^3J = 8.0 Hz, 1H, arom), 7.49−7.46 (m, 1H, arom), 7.39−7.35 (m, 2H, arom), 6.44 (dt, ^1J(P) = 473 Hz, ^3J = 4.0 Hz, 1H, P−*H*), 2.74−2.65 (m, 1H, C*H*), 2.45−2.36 (m, 1H, C*H*), 2.16 (s, 3H, CH_3 position 3), 2.15 (d, ^3J = 3.5 Hz, 3H, CH_3 position 2), 1.81 (d, ^3J(P) = 17 Hz, 3H, CH_3 position 1), 1.44 (ddd, ^3J(P) = 96.0 Hz, ^3J = 18.5 Hz, ^3J = 7.5 Hz, 6H, CH_3), 1.13 (ddd, ^3J(P) = 91.0 Hz, ^3J = 18.0 Hz, J = 7.0 Hz, 6H, CH_3). ^{13}C{^{1}H} NMR (125.77 MHz, $CDCl_3$): δ 145.1 (d, J = 3.8 Hz), 141.6, 138.9 (d, J = 8.0 Hz), 137.7 (d, J = 3.8 Hz), 129.8, 126.7, 123.5 (d, J = 3.5 Hz), 120.2, 51.5 (d, J = 32.6 Hz), 21.1 (d, J = 6.7 Hz), 20.8 (d, J = 5.6 Hz), 20.0 (d, J = 2.6 Hz), 19.9, 19.1 (d, J = 2.1 Hz), 18.2 (d, J = 2.3 Hz), 17.7 (d, J = 2.3 Hz), 11.1, 10.8. ^{31}P{^{1}H} NMR (202.46 MHz, $CDCl_3$): δ 36.6. ^{31}P NMR (202.46 MHz, $CDCl_3$): δ 36.6 (d, J = 472.9 Hz).

(1,2,3-Trimethylindenyl)dicyclohexylphosphonium Tetrafluoroborate (11·HBF$_4$). In a 100 mL Schlenk 1,2,3-trimethylindene (**4**; 2.44 g, 15.4 mmol) was dissolved in Et_2O (50 mL) under an argon atmosphere. The mixture was cooled to −60 °C (N_2/isopropyl alcohol), and *n*BuLi (5.9 mL, 2.5 M solution in hexane, 14.7 mmol) was added. The solution was stirred for 10 min at −60 °C and then for 3 h at ambient temperature. A white precipitate was formed. Then the mixture was cooled to −60 °C and Cy_2PCl (2.7 mL, 12 mmol) was added. The mixture was warmed to room temperature and stirred for additional 2 h, and the LiCl that formed was removed by filtration over a pad of Celite under Schlenk conditions. The resulting slightly yellowish filtrate was treated dropwise with HBF_4·Et_2O (2 mL, 14.9 mmol) to give a white precipitate, which was separated via filtration and dissolved in 10 mL of acetonitrile. After filtration the clear filtrate was dropped into Et_2O (900 mL, vigorously stirred). The white precipitate that formed was separated via suction filtration. Removal of the volatiles in vacuo afforded

11·HBF$_4$ as a white solid (2.82 g, 53%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.64 (d, ^3J = 7.5 Hz, 1H, arom), 7.48 (t, ^3J = 7.5 Hz, 1H, arom), 7.40−7.35 (m, 2H, arom), 6.36 (dt, ^1J(P) = 475 Hz, ^4J = 3.5 Hz, 1H, P−*H*), 2.34−2.26 (m, 1H, C*H*), 2.16 (d, ^4J(P) = 4.0 Hz, 3H, CH_3 position 2), 2.14 (s, 3H, CH_3 position 3), 2.09−1.14 (m, 21H, CH_2 and C*H*), 1.81 (d, ^3J(P) = 17.5 Hz, 3H, CH_3 position 1). ^{13}C{^{1}H} NMR (125.77 MHz, $CDCl_3$): δ 145.2 (d, J = 3.1 Hz), 141.8, 138.8 (d, J = 7.8 Hz), 137.8 (d, J = 2.9 Hz), 129.8, 126.7, 123.4, 120.0, 51.6 (d, J = 32.2 Hz), 31.0, 30.7 (d, J = 10.8 Hz), 30.5, 29.8 (d, J = 3.0 Hz), 29.0 (d, J = 3.5 Hz), 28.2 (d, J = 3.3 Hz), 28.1 (d, J = 3.1 Hz), 26.9 (d, J = 6.0 Hz), 26.8 (d, J = 5.8 Hz), 26.6, 26.5, 24.9 (d, J = 3.8 Hz), 19.6, 11.2, 10.7. ^{31}P{^{1}H} NMR (202.46 MHz, $CDCl_3$): δ 29.2. ^{31}P NMR (202.46 MHz, $CDCl_3$): δ 29.2 (d, J = 473.7 Hz).

(1,2,3,4,7-Pentamethylindenyl)diisopropylphosphonium Tetrafluoroborate (12·HBF$_4$). In a 100 mL Schlenk flask 1,2,3,4,7 pentamethylindene (**7**; 3.0 g, 16 mmol) was dissolved in Et_2O (50 mL) under an argon atmosphere. The mixture was cooled to −60 °C (N_2/isopropyl alcohol), and *n*BuLi (16.1 mL, 2.5 M solution in hexane, 15 mmol) was added. The solution was stirred for 10 min at −60 °C and then for 3 h at ambient temperature. A white precipitate was formed. The mixture was cooled to −60 °C, and *i*Pr$_2$PCl (2.0 mL, 12.8 mmol) was added. The mixture was warmed to room temperature and stirred for additional 2 h, and the LiCl that formed was removed by filtration over a pad of Celite under Schlenk conditions. The resulting slightly yellowish filtrate was treated dropwise with HBF$_4$·Et_2O (2.2 mL, 16 mmol) to give a white precipitate that was separated via filtration and dissolved in 10 mL of chloroform. After filtration the clear filtrate was dropped into Et_2O (900 mL, vigorously stirred). The white precipitate that formed was separated via suction filtration. Removal of the volatiles in vacuo afforded **12·HBF$_4$** as a white solid (4.23 g, 84%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.09 (d, ^3J = 8.0 Hz, 1H, arom), 6.97 (d, ^3J = 8.0 Hz, 1H, arom), 6.41 (dq, ^1J(P) = 468 Hz, ^3J = 5.3 Hz, 1H, P−*H*), 2.84−2.75 (m, 1H, C*H*), 2.59 (s, 3H, CH_3 benzylic), 2.58 (s, 3H, CH_3 benzylic), 2.31 (d, ^4J = 4.5 Hz, 3H, CH_3 position 2), 2.23−2.14 (m, 1H, C*H*), 2.13 (s, 3H, CH_3 position 3), 1.89 (d, ^3J(P) = 17 Hz, 3H, CH_3 position 1), 1.50 (ddd, ^3J(P) = 107 Hz, ^3J = 18.5 Hz, J = 7.0 Hz, 6H, CH_3), 1.12 (ddd, ^3J(P) = 96.5 Hz, ^3J = 18.5 Hz, J = 7.0 Hz, 6H, CH_3). ^{13}C{^{1}H} NMR (125.77 MHz, $CDCl_3$): δ 143.3, 141.4 (d, J = 9.2 Hz), 140.6, 136.2 (d, J = 6.3 Hz), 133.6, 132.2 (d, J = 2.1 Hz), 130.2, 130.0, 52.9 (d, J = 29.2 Hz), 22.1 (d, J = 3.6 Hz), 21.8, 20.7, 20.4 (d, J = 2.3 Hz), 20.2, 19.1 (d, J = 1.8 Hz), 18.9 (d, J = 1.9 Hz), 18.7 (d, J = 1.8 Hz), 18.1 (d, J = 3.1 Hz), 15.2, 12.3. ^{31}P{^{1}H} NMR (202.46 MHz, $CDCl_3$): δ 34.0. ^{31}P NMR (202.46 MHz, $CDCl_3$): δ 34.0 (d, J = 463 Hz).

(1,2,3,4,7-Pentamethylindenyl)dicyclohexylphosphonium Tetrafluoroborate (13·HBF$_4$). In a 100 mL Schlenk flask 1,2,3,4,7-pentamethylindene (**7**; 3.0 g, 16 mmol) was dissolved in Et_2O (50 mL) under an argon atmosphere. The mixture was cooled to −60 °C (N_2/isopropyl alcohol), and *n*BuLi (6.1 mL, 2.5 M solution in hexane, 15 mmol) was added. The solution was stirred for 10 min at −60 °C and then for 3 h at ambient temperature. A white precipitate was formed. Then the mixture was cooled to −60 °C and Cy_2PCl (2.8 mL, 12.7 mmol) was added. The mixture was warmed to room temperature and stirred for an additional 2 h at ambient temperature, and the LiCl that formed was removed by filtration over a pad of Celite under Schlenk conditions. The resulting slightly yellowish filtrate was treated dropwise with HBF$_4$·Et_2O (2.2 mL, 16 mmol) to give a white precipitate which was separated via filtration and dissolved in 10 mL of chloroform. After filtration the clear filtrate was dropped into Et_2O (700 mL, vigorously stirred). The white precipitate that formed was separated via suction filtration. Removal of the volatiles in vacuo afforded **13·HBF$_4$** as a white solid (4.12 g, 69%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.10 (d, ^3J = 8.0 Hz, 1H, arom), 6.97 (d, ^3J = 8.0 Hz, 1H, arom), 6.30 (dq, ^1J(P) = 470 Hz, J = 3.5 Hz, 1H, P−*H*), 2.58 (s, 3H, CH_3 benzylic), 2.58 (s, 3H, CH_3 benzylic), 2.46−2.39 (m, 1H, C*H*), 2.31 (d, ^4J(P) = 4.5 Hz, 3H, CH_3 position 2), 2.11 (s, 3H, CH_3 position 3), 1.89 (d, ^3J(P) = 16.5 Hz, 3H, CH_3 position 1), 1.86−0.93 (m, 21H, CH_2 and C*H*). ^{13}C{^{1}H} NMR (125.77 MHz, $CDCl_3$): δ 143.0, 140.9 (d, J = 9.3), 140.3, 136.0 (d, J = 4.9 Hz), 133.1, 131.9 (d, J = 4.0), 129.7, 129.6, 52.8 (d, J = 29.2 Hz), 31.5 (d, J = 7.2 Hz), 31.2, 29.6 (d, J = 3.5 Hz), 29.1 (d, J = 3.3 Hz), 28.2 (d, J = 3.5 Hz), 27.9 (d, J = 3.8 Hz), 27.0 (d, J = 11.9 Hz), 26.8, 26.7, 26.6 (d, J = 13.1), 25.0, 24.8, 20.2, 19.8, 18.1, 14.8, 11.9. ^{31}P NMR (202.46 MHz, $CDCl_3$): δ 25.5 (d, J = 472.3 Hz).

(4,7-Dimethoxy-1,2,3-trimethylindenyl)diisopropylphosphonium Tetrafluoroborate (14·HBF$_4$). In a 100 mL Schlenk flask 4,7-dimethoxy-1,2,3-trimethylindene (**9**; 1.7 g, 7.79 mmol) was dissolved in Et_2O (50 mL) under an argon atmosphere. The mixture was cooled to −60 °C (N_2/isopropyl alcohol), and *n*BuLi (3.0 mL, 2.5 M solution in hexane, 7.43 mmol) was added. The solution was stirred for 10 min at −60 °C and then for 3 h at ambient temperature. A white precipitate was formed. Then the mixture was cooled to −60 °C and *i*Pr$_2$PCl (1.0 mL, 6.24 mmol) was added. The mixture was warmed to room temperature and stirred for an additional 2 h at ambient temperature, and the LiCl that formed was removed by filtration over a pad of Celite under Schlenk conditions. The resulting slightly yellowish filtrate was treated dropwise with HBF$_4$·Et_2O (1 mL, 7.72 mmol) to give a white precipitate, which was separated via filtration and dissolved in 10 mL of chloroform. After filtration the clear filtrate was dropped into Et_2O (700 mL, vigorously stirred). The white precipitate that formed was separated via suction filtration. Removal of the volatiles in vacuo afforded **14·HBF$_4$** as a white solid (1.73 g, 66%). ^{1}H NMR (500 MHz, CD_3CN): δ 7.13 (dd, ^3J = 9.0 Hz, J = 1.5 Hz, 1H, arom), 6.99 (d, ^3J = 9.0 Hz, 1H, arom), 6.39 (dq, ^1J(P) = 465.5 Hz, ^3J = 3.0 Hz, 1H, P−*H*), 3.99 (s, 3H, O−CH_3), 3.87 (s, 3H, O−CH_3), 3.10−3.00 (m, 1H, C*H*), 2.62−2.51 (m, 1H, C*H*), 2.30 (dd, ^4J(P) = 5.0 Hz, J = 1.0 Hz, 3H, CH_3 position 2), 2.13 (s, 3H, CH_3 position 3), 1.86 (d, ^3J(P) =16.5 Hz, 3H, CH_3 position 1), 1.45 (ddd, ^3J(P) = 100 Hz, ^3J = 19 Hz, ^3J = 7.0 Hz, 6H, CH_3), 1.18 (ddd, ^3J(P) = 72.5 Hz, ^3J = 17.5 Hz, ^3J = 7 Hz, 6H, CH_3). ^{13}C{^{1}H} NMR (125.77 MHz, CD_3CN): δ 150.8 (d, J = 2.1 Hz), 150.4, 139.7 (d, J = 9.0 Hz), 137.6 (d, J = 3.4 Hz), 134.7 (d, J = 3.5 Hz), 130.5, 115.0, 110.5, 56.6, 56.1, 52.4 (d, J = 31.8 Hz), 23.4 (d, J = 35.8 Hz), 21.3 (d, J = 39.5 Hz), 19.9 (d, J = 2.64 Hz), 19.5 (d, J = 1.9 Hz), 19.0 (d, J = 2.9 Hz), 18.3 (d, J = 2.0 Hz), 17.7 (d, J = 2.3 Hz), 13.8, 10.8. ^{31}P NMR (202.46 MHz, CD_3CN): δ 33.1 (d, J = 464.8).

(4,7-Dimethoxy-1,2,3-trimethylindenyl)dicyclohexylphosphonium Tetrafluoroborate (15·HBF$_4$). In a 100 mL Schlenk flask 4,7-dimethoxy-1,2,3-trimethylindene (**9**; 1.7 g, 7.79 mmol) was dissolved in Et_2O (50 mL) under an argon atmosphere. The mixture was cooled to −60 °C (N_2/isopropyl alcohol), and *n*BuLi (3.0 mL, 2.5 M solution in hexane, 7.43 mmol) was added. A white precipitate was formed. The solution was stirred for 10 min at −60 °C and for 3 h at ambient temperature. Then the mixture was cooled to −60 °C and Cy_2PCl (1.3 mL, 6.19 mmol) was added. The mixture was warmed to room temperature and then for an additional 2 h at ambient temperature and the LiCl that formed was removed by filtration over a pad of Celite under Schlenk conditions. The resulting slightly yellowish filtrate was treated dropwise with HBF$_4$·Et_2O (1 mL, 7.79 mmol) to give a white precipitate, which was separated via filtration and dissolved in 10 mL of chloroform. After filtration the clear filtrate was dropped into Et_2O (700 mL, vigorously stirred). The white precipitate that formed was separated via suction filtration. Removal of the volatiles in vacuo afforded **15·HBF$_4$** as a white solid (1.72 g, 55%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.93 (dd, ^3J = 9.0 Hz, J = 1.5 Hz, 1H, arom), 6.77 (d, ^3J = 9.0 Hz, 1H, arom), 6.24 (ddd, ^1J(P) = 472.5, ^3J = 5.5 Hz, J

= 2.5 Hz, 1H, P−*H*), 3.92 (s, 3H, O−*CH*$_3$), 3.84 (s, 3H, O−*CH*$_3$), 2.60−2.49 (m, 1H, *CH*), 2.28 (dd, ^4J(P) = 4.0 Hz, J = 1.0 Hz, 3H, CH_3 position 2), 2.18−2.11 (m, 1H, *CH*), 2.06 (s, 3H, *CH*$_3$ position 3), 1.76 (d, ^3J(P) =16.5 Hz, 3H, *CH*$_3$ position 1), 2.04−1.01 (m, 20H, CH_2). $^{13}C\{^1H\}$ NMR (125.77 MHz, $CDCl_3$): δ 149.7 (d, J = 1.9 Hz), 149.5, 138.9 (d, J = 7.0), 136.9 (d, J = 3.0 Hz), 134.2 (d, J = 2.8), 129.7, 113.8, 109.1, 56.3, 55.7, 51.6 (d, J = 32.2 Hz), 32.3, 32.0, 30.6, 30.3, 29.3(d, J = 3.3 Hz), 29.2 (d, J = 5.3 Hz), 28.2 (d, J = 3.3 Hz), 27.7 (d, J = 3.1 Hz), 27.0 (d, J = 13.1 Hz), 26.9 (d, J = 14.2 Hz), 25.1, 24.9, 17.8, 13.6, 10.7. $^{31}P\{^1H\}$ NMR (202.46 MHz, $CDCl_3$): δ 25.4. ^{31}P NMR (202.46 MHz, $CDCl_3$): δ 25.4 (d, J = 471.1 Hz).

Cp*PCy$_2$·HBF$_4$ (17·HBF$_4$). In a 250 mL Schlenk flask pentamethylcyclopentadiene (HCp* (**16**);[98] 2.9 g, 21.3 mmol) was dissolved in diethyl ether (100 mL) and treated with *n*BuLi (8.1 mL, 2.5 M in hexane, 20.3 mmol) at −60 °C. The mixture was stirred for 4 h at ambient temperature, to give a thick white suspension. THF (absolute, 100 mL) was added, and the suspension was quenched with Cy_2PCl (3.93 g, 16.9 mmol) at −60 °C. The reaction mixture was stirred at ambient temperature overnight and filtered over a small pad of Celite. The clear, colorless filtrate was then quenched with HBF_4·Et_2O (2.7 mL, 19.9 mmol), which led to precipitation of the phosphonium salt as a white solid about 3 min after the addition of the acid. The solid was separated via suction filtration and washed with Et_2O, and the volatiles were removed in vacuo to afford **17·HBF$_4$** as a white solid (3.7 g, 52%). ^1H NMR (500 MHz, $CDCl_3$): δ 6.06 (dt, ^1J(PH) = 470 Hz, ^3J = 4 Hz, 1 H, P*H*), 2.15−2.07 (m, 2 H, *CH*), 2.03−1.99 (m, 2 H, CH_2), 1.98 (s, 6 H, *CH*$_3$), 1.89 (d, ^4J(PH) = 3.5 Hz, 6 H, *CH*$_3$), 1.89−1.85 (m, 6 H, CH_2), 1.73−1.56 (m, 6 H, CH_2), 1.51 (d, ^3J(PH) = 17.5 Hz, 3 H, *CH*$_3$), 1.32−1.25 (m, 6 H, CH_2). $^{13}C\{^1H\}$ NMR (125.75 MHz, $CDCl_3$): δ 142.7 (d, J(P−C) = 6.8 Hz), 134.8, 55.1 (d, J(P−C) = 28.3 Hz), 30.3, 30.0, 29.6 (d, J(P−C) = 3.5 Hz), 28.5 (d, J(P−C) = 3.4 Hz), 26.9 (d, J(P−C) = 11.9 Hz), 26.7 (d, J(P−C) = 13.6 Hz), 25.0, 17.3 (d, J(P−C) = 3.3 Hz), 11.4 (d, J(P−C) = 22.1 Hz). ^{31}P NMR (202.45 MHz, $CDCl_3$): δ 26.7 (d, J(P−H) = 471.5 Hz).

Cp*P*i*Pr$_2$·HBF$_4$ (18·HBF$_4$). In a 250 mL Schlenk flask pentamethylcyclopentadiene (HCp* (**16**); 2.79 g, 20.5 mmol) was dissolved in diethyl ether (absolutely, 175 mL) and treated with *n*BuLi (7.8 mL of a 2.5 M solution in hexane, 19.5 mmol) at −60 °C. The mixture was stirred for 4 h at ambient temperature (magnetic stirrer), resulting in a thick white suspension. THF (absolute, 50 mL) was added, followed by *i*Pr$_2$PCl (2.48 g, 16.25 mmol) at −60 °C. The reaction mixture was stirred at ambient temperature overnight and filtered over a small pad of Celite. The clear, colorless filtrate was quenched with HBF_4·Et_2O (2.76 mL, 20.3 mmol), which led to precipitation of the phosphonium salt as a white solid. The solid was separated via suction filtration and washed with Et_2O, and the volatiles were removed in vacuo to afford **18·HBF$_4$** as a white solid (5.2 g, 94%). ^1H NMR (500 MHz, $CDCl_3$): δ 6.21 (dt, ^1J(PH) = 468.5 Hz, ^3J = 4.5 Hz, 1 H, P*H*), 2.52−2.43 (m, 2 H, *CH*), 2.00 (s, 6 H, *CH*$_3$), 1.89 (d, ^4J(PH) = 3.0 Hz, 6 H, *CH*$_3$), 1.51 (d, ^3J(PH) = 17.5 Hz, 3 H, *CH*$_3$), 1.47 (dd, ^3J(PH) = 18.5 Hz, ^3J = 7.0 Hz, 6 H, *CH*$_3$), 1.38 (dd, ^3J(PH) = 18 Hz, ^3J = 7.5 Hz, 6 H, *CH*$_3$). $^{13}C\{^1H\}$ NMR (125.75 MHz, $CDCl_3$): δ 143.2 (d, J(P−C) = 6.7 Hz), 135.0, 55.2 (d, J(P−C) = 29.2 Hz), 20.8 (d, J(P−C) = 38.4 Hz), 20.1 (d, J(P−C) = 2.5 Hz), 18.8 (d, J(P−C) = 3.3 Hz), 18.1 (d, J(P−C) = 3.4 Hz), 11.8 (d, J(P−C) = 39.4 Hz). $^{31}P\{^1H\}$ NMR (202.45 MHz, $CDCl_3$): δ 34.9. ^{31}P NMR (202.45 MHz, $CDCl_3$): δ 34.9 (d, J(P−H) = 469.3 Hz).

General Procedure for the Synthesis of Phosphines from the Respective Phosphonium Salts. The phosphonium salt was first dissolved in the minimum amount of CH_2Cl_2, and then Et_3N (10 equiv per phosphonium group) was added. After the mixture was stirred for 30 min, twice the volume of Et_2O was added to quantitatively precipitate the Et_3NH^+ salt. Following the filtration of the precipitates, the volatiles were evaporated from the filtrate. The remaining material is pure phosphine, typically formed in quantitative yields.

General Procedures for the Cross-Coupling Reactions. All cross-coupling reactions are carried out under an argon atmosphere in deaerated solvents (*freeze and thaw*).

Suzuki Reaction of Aryl Chlorides (in Dioxane). (a) Preparation of the Catalyst Stock Solution. Na_2PdCl_4 (0.05 mmol), phosphonium salt (0.1 mmol), and Cs_2CO_3 (0.2 mmol) were placed in a Schlenk tube. Dioxane (5.0 mL) was added, and the mixture was stirred at 45 °C for 2 h until the solution turned off-white. This stock solution had a concentration of 0.01 M in [Pd].

(b) Cross-Coupling Reaction. To the aryl chloride (1 mmol) were added boronic acid (1.5 mmol), Cs_2CO_3 (2 mmol), dioxane (5 mL), and the catalyst stock solution. The reaction mixture was stirred at 100 °C in an aluminum block. After it was cooled to room temperature, the reaction mixture was diluted with ether (15 mL) and washed with water (10 mL) and the organic phase was dried over $MgSO_4$, filtered, and concentrated in vacuo. The product was isolated by column chromatography (silica, cyclohexane−ethyl acetate (100:2)). Alternatively, the yield was determined via gas chromatography with hexadecane or diethylene glycol di-*n*-butyl ether as an internal standard.

Sonogashira Reaction of Aryl Chlorides (in dmso). Dry dmso (5 mL, crown cap), aryl chloride (1.5 mmol), acetylene (2.1 mmol), and Na_2CO_3 (3 mmol) were placed in a Schlenk tube. Then the catalyst was added in the given concentration, Na_2PdCl_4−ligand (phosphonium salt)−CuI (4:8:3), under argon. The reaction mixture was stirred at 100−120 °C in an aluminum block for 12−20 h. After it was cooled to room temperature, the reaction mixture was diluted with ether (15 mL) and washed with water (10 mL) and the organic phase was dried over $MgSO_4$, filtered, and concentrated in vacuo. The product was isolated by column chromatography (silica, cyclohexane−ethyl acetate (100:2)). Alternatively, the yield was determined via gas chromatography with hexadecane or diethylene glycol di-*n*-butyl ether as an internal standard.

Buchwald−Hartwig Amination of Aryl Chlorides (in Toluene). Dry toluene (5 mL), aryl chloride (5 mmol), amine (6 mmol) and NaO*t*Bu (6 mmol) were placed in a Schlenk tube. Next the catalyst was added in the given concentration, followed by Na_2PdCl_4/ligand (phosphonium salt) (1:2). The reaction mixture was stirred at 120 °C in an aluminum block. After it was cooled to room temperature, the reaction mixture was diluted with ether (15 mL) and washed with water (10 mL) and the organic phase was dried over $MgSO_4$, filtered, and concentrated in vacuo. The product was isolated by column chromatography (silica, cyclohexane−ethyl acetate (90:10)). Alternatively, the yield was determined via GC with hexadecane or diethylene glycol di-*n*-butyl ether as an internal standard.

***N*-Ferrocenyl-4-methoxyaniline (19).** ^1H NMR (500 MHz, $CDCl_3$): δ 6.89 (d, ^3J = 9.0 Hz, 2 H, *CH*, ar), 6.81 (d, ^3J = 9.0 Hz, 2 H, *CH*, ar), 4.61 (s (br), 1 H, N*H*), 4.16 (s, 7 H, Fc), 3.99 (s, 2 H, Fc), 3.77 (s, 3 H, *CH*$_3$). $^{13}C\{^1H\}$ NMR (125.77 MHz, $CDCl_3$): δ 153.3, 139.5, 117.2, 114.6, 102.8, 68.7, 64.1, 60.4, 55.7. CV: $E_{1/2}$ = 0.142 V; ΔE = 76 mV. HRMS (*m*/*z*): calcd for $C_{17}H_{17}NOFe$, 307.0659, found, 307.06654.

***N*-Ferrocenyl-3-(trifluoromethyl)aniline (20).** ^1H NMR (500 MHz, $CDCl_3$): δ 7.27−7.24 (m, 2 H, ar), 7.01 (d, ^3J = 7.5 Hz, 1 H, *CH*, ar), 6.95 (dd, ^3J = 8.0 Hz, J = 2.0 Hz, 1 H, *CH*, ar), 5.10 (s (br), 1 H, N*H*), 4.23 (t, ^3J = 2.0 Hz, 2 H, Fc), 4.20 (s, 5 H, Fc), 4.07 (t, ^3J = 1.5 Hz, 2 H, Fc). $^{13}C\{^1H\}$ NMR (125.77 MHz, $CDCl_3$): δ 146.5, 131.4 (q, ^2J = 31.2 Hz, *C*−CF_3, ar), 129.5, 125.8 (q, ^1J = 273.3 Hz, CF_3), 117.4, 114.8 (q, ^3J = 4.8 Hz), 110.6 (q, ^3J = 4.1 Hz), 98.7, 69.0, 64.9, 62.4. CV: $E_{1/2}$ = 0.268 V; ΔE = 72 mV). HRMS (*m*/*z*): calcd for $C_{17}H_{14}NF_3Fe$, 345.0427; found, 345.04401.

Acknowledgment. We wish to thank the "Fonds der Chemischen Industrie" and the "Studienstiftung des Deutschen Volkes" for a fellowship to C.A.F., Degussa AG and Provadis, Partner für Bildung und Beratung GmbH for financial support, and cand.-chem. Julio Lado-Garrido for experimental assistance.

Note Added after ASAP Publication. In the version of this paper published on the Web on April 11, 2007, the two boldface paragraph heads in the right-hand column of the third page were incorrect. The version that now appears is correct.

Note Added in Proof. After submission of the manuscript a copper catalyzed amination of ferrocenyl iodide was reported: Özçubukçu, S.; Schmitt, E.; Leifert, A.; Bolm, C. *Synth.* **2007**, 389.

Supporting Information Available: Figures giving NMR spectra of the new products and cyclic voltammograms of the ferrocenes. This material is available free of charge via the Internet at http://pubs.acs.org.

OM070094M

4.3. Erfolgreiches Upscaling: Darstellung von 9-Alkylfluorenyl-phosphinen

Der Inhalt dieses Kapitels wurde bereits veröffentlicht:

Christoph A. Fleckenstein, Renat Kadyrov, Herbert Plenio, *"Efficient Large Scale Synthesis of 9-Alkylfluorenyl Phosphines for Pd-Catalyzed Cross Coupling Reactions"*, *Org. Process Res. Dev.* **2008**, *12*, 475-479.

Als ein entscheidendes Kriterium für die Entwicklung einer industriell nutzbaren Ligandenklasse wurde im einleitenden Teil dieser Arbeit die Verfügbarkeit der Liganden definiert. Für industrielle Anwendungen muss ein Ligand auf möglichst einfache Weise im Multikilogramm-Maßstab darstellbar sein. In diesem Kapitel wird das Upscaling der Dialkylfluorenylphosphine beschrieben.

Die bisher beschriebene Laborsyntheseroute erwies sich als ungeeignet für die Ligandsynthese in größeren Mengen. Im technischen Maßstab verlief die Synthese zum 9-Alkylfluoren durch Deprotonierung von Fluoren mit *n*BuLi unselektiv. Aufgrund von Umprotonierungen wurde neben dem Produkt noch Dialkylfluoren sowie Edukt erhalten (Abb. 65). Eine einfache Trennung der drei Verbindungen konnte nicht erreicht werden. Änderungen der Reaktionstemperatur, der Base oder des Solvens trugen ebenfalls nicht zur Lösung des Problems bei.

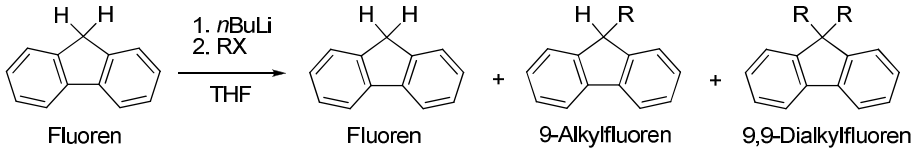


Abbildung 65. Unselektive Alkylierung von Fluoren im Kilomaßstab.

Die selektive Monoalkylierung von Fluoren im technischen Maßstab konnte schließlich durch folgende Modifikation erreicht werden (Abb. 66): Die basisch katalysierte Kondensation von Fluoren mit dem entsprechenden Alkylaldehyd und anschließender Transferhydrierung durch den entsprechenden Alkohol liefert das gewünschte 9-Monoalkylfluoren in hoher Ausbeute. Die weitere Synthese zum leicht isolierbaren Phosphoniumsalz war mit geringfügigen Änderungen von der Laborsynthese auf den großen Maßstab übertragbar.

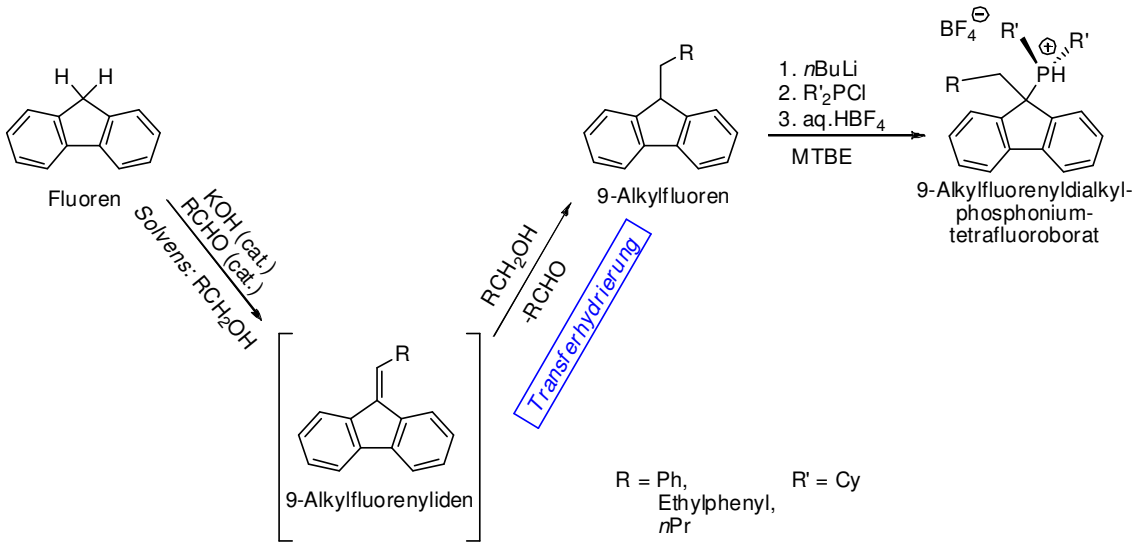


Abbildung 66. Syntheseroute zur Darstellung von Fluorenyldialkylphosphinen im technischen Maßstab.

Die Vorteile des neuen Verfahrens sind:

- effiziente und selektive Syntheseroute der 9-Alkylfluorenyldialkylphosphine im Kilogramm-Maßstab
- Einsatz preiswerter Edukte und Reagenzien
- Gesamtausbeute >80 %; Reinheit >>99 %
- bequeme Isolation der Produkte als stabile Phosphoniumsalze

Mit dem entwickelten optimierten Syntheseverfahren wurden drei verschiedene Fluorenylphosphoniumsalze in größerem Maßstab (mehrere 100 g) dargestellt.

Organic Process Research & Development **2008**, *12*, 475–479

Full Papers

Efficient Large-Scale Synthesis of 9-Alkylfluorenyl Phosphines for Pd-Catalyzed Cross-Coupling Reactions

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Abstract:

The reactions of aliphatic alcohols with fluorene coupled with a transfer hydrogenation result in the facile formation of 9-alkylfluorenes, whose deprotonation with *n*BuLi and quenching of the fluorenyl anion with Cy_2PCl in MTBE gave 9-alkylfluorenyldicyclohexyl phosphines, which are conveniently isolated as the respective phosphonium tetrafluoroborates after treatment with aqueous HBF_4. This route enables the facile large-scale (kilogram) synthesis of new ligands highly effective in Pd-catalyzed cross-coupling reactions.

Introduction

Pd-catalyzed cross-coupling reactions have become valuable tools in the production of fine chemicals.[1–5] The significant interest in this chemistry for industrial applications is documented in a large number of patents, which were recently compiled and reviewed by Corbet and Mignani.[6] Selected examples for applications of cross-coupling reactions include the Sonogashira reaction for the synthesis of an antimitotic agent (Novartis)[7] or tazarotene,[8] the Buchwald–Hartwig coupling in the hydrazonation of aromatic chlorides (Rhodia),[9] the Negishi coupling for a pyrimidine-based PDE-V inhibitor (Johnson & Johnson),[10] and the synthesis of the oncology candidate CP-724,714 (Pfizer).[11]

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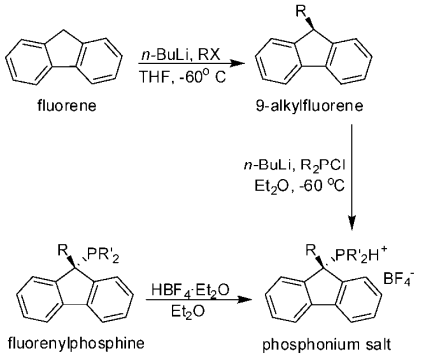
(1) Zapf, A.; Beller, M. *Top. Catal.* **2002**, *19*, 101.
(2) Blaser, H.-U.; Indolese, A.; Naud, F.; Nettekoven, U.; Schnyder, A. *Adv. Synth. Catal.* **2004**, *346*, 1583.
(3) Larsen, R. D. *Organometallics in Process Chemistry*; Springer Verlag: New York, 2004.
(4) Schlummer, B.; Scholz, U. *Adv. Synth. Catal.* **2004**, *346*, 1599.
(5) Buchwald, S. L.; Mauger, C.; Mignani, G.; Scholz, U. *Adv. Synth. Catal.* **2006**, *348*, 23.
(6) Corbet, J.-P.; Mignani, G. *Chem. Rev.* **2006**, *106*, 2651.
(7) Königsberger, K.; Chen, G.-P.; Wu, R. R.; Girgis, M. J.; Prasad, K.; Repic, O.; Blacklock, T. J. *Org. Process Res. Dev.* **2003**, *7*, 733.
(8) Frigoli, S.; Fuganti, C.; Malpezzi, L.; Serra, S. *Org. Process Res. Dev.* **2005**, *9*, 646.
(9) Mauger, C. C.; Mignani, G. A. *Org. Process Res. Dev.* **2004**, *8*, 1065.
(10) Pérez-Balado, C.; Willemsens, A.; Ormerod, D.; Aelterman, W.; Mertens, N. *Org. Process Res. Dev.* **2007**, *11*, 237.
(11) Ripin, D. H. B.; Bourassa, D. E.; Brandt, T.; Castaldi, M. J.; Frost, H. N.; Hawkins, J.; Johnson, P. J.; Massett, S. S.; Neumann, K.; Phillips, J.; Raggon, J. W.; Rose, P. R.; Rutherford, J. L.; Sitter, B.; Stewart, A. M.; Vetelino, M. G.; Wei, L. *Org. Process Res. Dev.* **2005**, *9*, 440.

Scheme 1. **Small-scale synthesis of 9-alkylfluorenyl phosphines**



Usually, high activity catalysts for Pd-mediated coupling reactions require sterically demanding and electron-rich phosphines,[12] which need to be available in sufficient amounts to allow the production of commercial products.[13] We have recently reported the synthesis of 9-fluorenyl based phosphines, which are versatile ligands for various cross-coupling reactions.[14,15]

The published small-scale synthesis of 9-alkyl-fluorenyldialkylphosphines and their respective phosphonium salts is depicted in Scheme 1. Starting from commercially available fluorene, deprotonation with *n*BuLi in THF at −60 °C and subsequent quenching of the fluorenide with alkyl halides afforded the respective 9-alkylfluorene. In the second step the 9-alkylated fluorene was deprotonated with *n*BuLi in diethylether at −60 °C and quenched with Cy_2PCl to result in the formation of the respective fluorenyl phosphine, which was conveniently isolated as the phosphonium salt after treatment of the free phosphine with $HBF_4 \cdot Et_2O$. This route is useful for the small-scale synthesis of such phosphines and renders up to 10 g of various 9-alkylfluorenylphosphines, which were isolated as phosphonium salts in yields of 70–90%. For the large-scale synthesis (several hundred grams to kilograms) of such phosphines, the present setup is inconvenient. First of all the yields of the overall reactions need to be improved, and additional problems such as the use of less favourable solvents (diethyl-

(12) an der Heiden, M.; Plenio, H. *Chem. Commun.* **2007**, 972.
(13) Kaye, S.; Fox, J. M.; Hicks, F. A.; Buchwald, S. L. *Adv. Synth. Catal.* **2001**, *343*, 789.
(14) Fleckenstein, C. A.; Plenio, H. *Chem.–Eur. J.* **2007**, *13*, 2701.
(15) Fleckenstein, C. A.; Plenio, H. *Organometallics* **2007**, *26*, 2758.

10.1021/op7001479 CCC: $40.75
Published on Web 01/01/2008

ether), the application of highly flammable $HBF_4 \cdot Et_2O$, and the need for low temperatures (−60 °C) for the *n*BuLi reactions need to be dealt with.

We describe herein an optimized, large-scale synthesis of various 9-alkyl-fluorenyl phosphonium salts.[16]

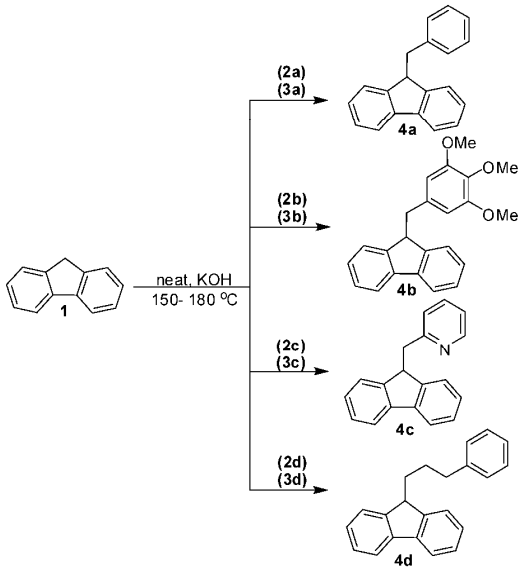
Improved Synthesis of 9-Alkylated Fluorenes

The decisive observation that forced us to look for improvements in the synthesis of 9-alkylated fluorenes was the unexpected formation of significant amounts of 9,9-dialkylated fluorenes (up to 30%) on quenching the fluorenyl anion with alkyl halides in large-scale reactions (>50 g). This is in stark contrast to the results of the small-scale synthesis (<5 g) which produces virtually quantitative yields of the 9-alkylated fluorenes. These problems partially originate from the increased concentration of reactants in the reaction mixture. In combination with the relatively faster addition of the alkyl halide to the metalated fluorene and the small differences in the CH-acidity of fluorene and 9-alkylated fluorene, the irreversible formation of the dialkylated product (up to 30% yield) becomes a major problem in the upscaling of this reaction. Furthermore, the separation of the resulting mixture of fluorene and mono- and dialkylated fluorenes by recrystallisation was impracticable owing to similar solubility properties. In conclusion, we were forced to look for alternative pathways, as the small-scale route is not feasible for the synthesis of bulk amounts.

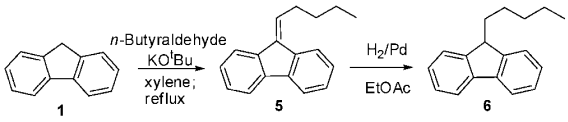
The literature offers other synthetic pathways for the preparation of 9-alkylfluorenes, such as the condensation of fluorene and alcohols with sodium metal at elevated temperatures[17–19] or the formation of alkylidenefluorenes via condensation of fluorene and aldehydes and their subsequent hydrogenation.[20–22] According to Sprinzak[23] the direct benzylation of fluorene with benzylalcohol containing small amounts of benzaldehyde initially leads to the formation of benzylidenefluorene, which at elevated temperatures (ca. 230 °C) undergoes transfer hydrogenation with benzylalcohol. This route was used by Sprinzak, affording 5–10 g of 9-benzylfluorene.

We decided to test the Sprinzak approach for the large-scale synthesis of 9-benzylfluorenes and to generalize this method. Accordingly, 9-benzylfluorene (**4a**) was synthesized on a 300 g scale in benzylalcohol (**2a**) without additional solvent. By deliberate addition of a substoichiometric amount (ca. 10%) of benzaldehyde (**3a**), the reaction temperature was lowered to 150 °C.[24] The white crystalline product thus formed in near quantitative yield and excellent purity does not require additional purification. This method could be generalized for the synthesis of various 9-benzylated fluorenes, whose Pd complexes turn out to be highly active catalysts for various carbonylation

Scheme 2. **Synthesis of 9-alkylated fluorenes**



Scheme 3. **Two-step synthesis of 9-alkylated fluorene via alkylidenes**



reactions:[25] Benzylalcohols bearing electron-rich substituents such as 3,4,5-trimethoxybenzylalcohol (**2b**) were reacted with fluorene in the same manner as electron-deficient building blocks such as 2-pyridinemethanol (**2c**) (Scheme 2). The resulting 2-(9*H*-fluoren-9-ylmethyl)-pyridine (**4c**) is an interesting building block for potential N,P bidentate ligands; the facile multigram synthesis reported here provides easy access to this compound.

The value of this synthetic approach could be extended significantly with the successful transformation of aliphatic alcohols other than benzylic alcohols. Fluorene was reacted with 3-phenyl-propan-1-ol (**2d**) employing the improved Sprinzak conditions. Raising the reaction temperature to 185 °C resulted in the formation of the respective 9-alkylated flourene **4d** in near quantitative yield on 400 g scale. Obviously, this method is suitable for the bulk production of a broad variety of 9-monoalkylated fluorenes and easily extendable to multikilogram production.

A modified approach was, however, needed for short chain aliphatic alcohols and aldehydes having low boiling points. Such aldehydes were reacted directly with fluorene to produce the respective alkylidene using the method of Bachmann and Polansky.[21] For safety reasons elemental potassium was successfully replaced by KO'Bu.

In this manner 9-butylidenefluorene (**5**) was isolated in 63% yield and >99% purity as a white solid, which was directly introduced into the next step (Scheme 3). The following hydrogenation of **5** to the respective 9-*n*-butylfluorene (**6**) has

(16) The ligands are now commercially available by Strem and Degussa Homogeneous Catalysts under the tradename cataCXium F.
(17) Douris, J.; Mathieu, A. *Bull. Soc. Chim. Fr.* **1973**, *2*, 709.
(18) Schoen, K. L.; Becker, E. I. *J. Am. Chem. Soc.* **1955**, *77*, 6030.
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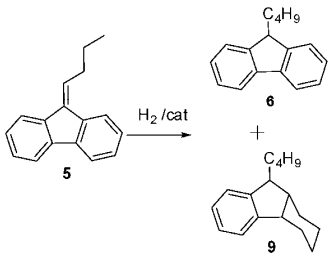
(20) Schultz, R. F.; Smullin, C. F. *J. Am. Chem. Soc.* **1940**, *12*, 2904.
(21) Bachman, G. B.; Polansky, S. *J. Org. Chem.* **1951**, *16*, 1690.
(22) Wawzonek, S.; Duffek, E.; Sial, N. M. *J. Org. Chem.* **1956**, *21*, 276.
(23) Sprinzak, Y. *J. Am. Chem. Soc.* **1956**, *78*, 466.
(24) Further experiments for reduction of reaction temperature with transfer hydrogenation catalysts like Rh- or Ru-phosphine complexes or the addition of HCOOH/HCOOLi did not result in further improvements.

(25) Fleckenstein, C. A.; Almena, J.; Plenio, H. Unpublished work.

Scheme 4. **Synthesis of 9-alkylated fluorenederivatives via hydrogenation**



already been reported using Pd on charcoal or PtO_2 as catalysts.[17,22] The reported yields of only 75–90% and the need for distillative workup required improvements. However, initial hydrogenation experiments utilizing 10% Pd on activated charcoal (10 bar H_2 pressure, room temperature) produced an impurity of **9** in 10% yield, in which one aromatic ring was hydrogenated (Scheme 4). Changing the catalyst to PtO_2 and applying only 5 bars of H_2 at 25 °C reduced the amount of **9** to 3%. The use of 5% Pd on activated charcoal, 2 bar H_2 in technical grade ethyl acetate gave **6** in >99% yield without detectable impurities.

9-Alkylfluorenyl Phosphonium Tetrafluoroborates

Improved conditions were also developed for the phosphination of 9-alkylfluorenes. The deprotonation of the 9-alkylfluorene is now performed in MTBE instead of diethylether with a stoichiometric amount of *n*BuLi at 0 °C instead of −60 °C as previously reported. Addition of Cy_2PCl (**7**) leads to smooth carbon-phosphorous bond formation at room temperature. The removal of the formed LiCl was easily achieved by a simple washing of the MTBE-LiCl suspension with deaerated water. The formation and the precipitation of the phosphonium salt were accomplished by addition of 48% aqueous HBF_4 to the MTBE solution. Again the use of hazardous diethylether was avoided. Other ethereal solvents are not suitable as the respective phosphonium salts do not precipitate from THF or dioxane. The resulting 9-alkylfluorenyl phosphonium tetrafluoroborates were isolated as white crystals following a simple filtration. The phosphonium salts are air-stable and storable equivalents of the desired phosphines, which are liberated under the basic conditions of the cross-coupling experiment.[26,27]

Applying this improved synthetic route the phosphonium salts **8a**, **8b**, and **8c** (Scheme 5) were produced on a 200–250 g scale in >95% overall yield and ≫99% purity.

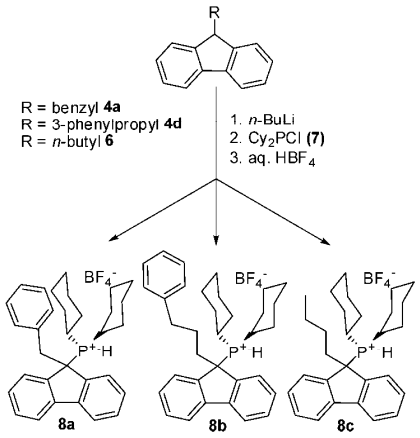
Summary

We have reported a significantly improved large-scale synthesis of 9-alkylfluorenylphosphines. Following an in situ deprotonation of the respective phosphonium salts, the obtained phosphines are useful as ligands for a variety of palladium-catalyzed coupling reactions.

Experimental Section

General Experimental. All chemicals were purchased as reagent grade from commercial suppliers and used without further purification, unless otherwise noted. Fluorene was purchased from Fluka (purity >99%). For the hydrogenation of *n*-butylidenefluorene Pd on carbon (5%) from Aldrich was used. *n*-Butyllithium (2.5 M in hexane) was purchased from Acros. MTBE was purchased from Fluka as crown cap-quality and used without any further deaeration treatment for the phosphine syntheses. Water used in phosphine syntheses for extraction of LiCl was deaerated with argon (20 min). Proton (^{1}H NMR), carbon (^{13}C NMR), nitrogen (^{15}N NMR), and phosphorus (^{31}P NMR) nuclear magnetic resonance spectra were recorded on a Bruker DRX 500 instrument at 500, 125.75, 50.69, and 202.46 MHz, respectively at 293 K. The chemical shifts are given in parts per million (ppm) on the delta scale (δ) and are referenced to tetramethylsilane (δ = 0 ppm), ^{1}H NMR and 65% aqueous H_3PO_4, (δ = 0 ppm), ^{31}P NMR nitromethane (δ = 0 ppm), ^{15}N NMR. Abbreviations for NMR data: s = singlet; d = doublet; t = triplet; q = quartet; qi = quintet; dd = doublet of doublets; dt = doublet of triplets; dq = doublet of quartets; tt = triplet of triplets; m = multiplet. Mass spectra were recorded on a Finigan MAT 95 magnetic sector spectrometer. GC experiments were run on a Clarus 500 GC with autosampler and FID detector. Column: Varian CP-Sil 8 CB (l = 15 m, d_i = 0.25 mm, d_F = 1.0 μm), N_2 (flow 17 cm/s; split 1:50); injector temperature 270 °C, detector temperature 350 °C. Temperature program: isotherm 150 °C for 5 min, heating to 300 °C with 25 °C/min, isotherm for 15 min.

Scheme 5. **Formation of 9-alkylfluorenyl phosphonium salts**



9-Benzyl-9*H*-fluorene (4a). In a 1-L 2-necked round-bottomed flask was suspended fluorene (**1**) (200 g, 1.20 mol) in benzyl alcohol (**2a**) (480 mL, 4.64 mol) and benzaldehyde (**3a**) (72 mL, 0.71 mol). KOH pellets (96 g, 1.71 mol) were added, and the mixture was stirred at 150 °C for 2.5 h. During the reaction the color changed from yellow to red, then to yellow, and finally to off white. The stirred reaction mixture was cooled to 95 °C, water (400 mL) was added, and the mixture was cooled to room temperature and stirred for another 0.5 h to obtain a white suspension. The product was separated via filtration (glass frit G3), washed with water (3 × 200 mL), recrystallized from EtOH/*i*-propanol and dried at 50 °C in vacuo to afford 9-benzyl-9*H*-fluorene (**4a**) (285 g, 93%) as white

(26) an der Heiden, M.; Plenio, H. *Chem.—Eur. J.* **2004**, *10*, 1789.
(27) Remmele, H.; Köllhofer, A.; Plenio, H. *Organometallics* **2003**, *22*, 4098.

crystals. Purity (GC/NMR): >99%. ^{1}H and ^{13}C NMR spectra were identical with the literature.[14,28]

9-(3,4,5-Trimethoxybenzyl)-9*H*-fluorene (4b). In a 250-mL 2-necked round-bottomed flask was suspended fluorene (**1**) (20 g, 0.120 mol) in 3,4,5 trimethoxybenzyl alcohol (**2b**) (50 mL, 0.311 mol) and 3,4,5-trimethoxybenzaldehyde (**3b**) (5.0 g, 0.025 mol). KOH pellets (10 g, 0.178 mol) were added, and the mixture was stirred at 185 °C for 3 h. During the reaction the mixture changed its colour from yellow to dark brown and finally to cream (after 20 min). The stirred reaction mixture was cooled to 95 °C, water (125 mL) was added, and the mixture was cooled to room temperature and stirred for another 0.5 h to get a suspension. The product was separated via filtration (glass frit G3) and washed with water (3 × 75 mL), giving a beige crude product. This crude product was recrystallized from hot EtOH using 1 g of charcoal to decolorize affording 9-(3,4,5-trimethoxybenzyl)-9*H*-fluorene (**4b**) (36.8 g, 89%) as off-white crystals. Purity (GC/NMR): > 99%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, ^3J = 7.5 Hz, 2 H, *CH*, ar), 7.33 (ddt, J = 0.5 Hz, ^4J = 1.5 Hz, ^3J = 7.5 Hz, 2 H, *CH*, ar), 7.27–7.20 (m, 4 H, C*H*, ar), 6.34 (s, 2 H, *CH*, ar), 4.20 (t, ^3J = 7.0 Hz, 1 H, 9-Flu *H*), 3.83 (s, 3 H, OCH_3), 3.73 (s, 6 H, OCH_3), 3.07 (d, ^3J = 7.0 Hz, 2 H, CH_2); ^{13}C{^{1}H} NMR (125.8 MHz, $CDCl_3$) δ 153.3, 147.0, 141.4, 136.9, 135.4, 127.6, 127.0, 125.3, 120.3, 106.9, 61.3, 56.5, 49.1, 40.6; HRMS calcd for $C_{23}H_{22}O_3$ 346.1568, found 346.15881.

2-(9*H*-Fluoren-9-ylmethyl)-pyridine (4c). In a 500-mL 2-necked round-bottomed flask was suspended fluorene (**1**) (37.4 g, 0.225 mol) in 2-pyridinemethanol (**2c**) (90 mL, 0.926 mol) and 2-pyridinecarbaldehyde (**3c**) (12.8 g, 0.141 mol). KOH pellets (18 g, 0.321 mol) were added, and the mixture was stirred at 185 °C for 2 h. The stirred reaction mixture was cooled to 100 °C, water (125 mL) was added, and the mixture was cooled to room temperature and stirred for another 0.5 h. The product was suspended as slightly turquoise pellets in the reaction mixture. The crude product was separated via filtration (glass frit G3) and washed with water (3 × 75 mL). The crude product was dissolved in a mixture of ice (700 g) and concentrated HCl (200 mL). The solution was extracted with methylene chloride (400 mL) to remove remaining **2c** and **3c** (**4c**•HCl is to be found in the organic phase). The organic layer was brought to pH 9 with NaOH, washed with water (2 × 200 mL), and dried over $MgSO_4$. The volatiles were stripped off from the clear colourless filtrate at 50 °C in vacuo to afford **4c** (55 g, 95%) as white crystals. Purity (GC/NMR): >99%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.68 (dq, ^3J = 5.0 Hz, J = 1.0 Hz, 1 H, *CH*, ar), 7.74 (dt, ^3J = 7.5 Hz, J = 1.0 Hz, 2 H, *CH*, ar), 7.59 (td, ^3J = 7.5 Hz, J = 2.0 Hz, 1 H, *CH*, ar), 7.33 (tt, ^3J = 7.5 Hz, J = 1.0 Hz, 2 H, *CH*, ar), 7.22–7.17 (m, 3 H, C*H*, ar), 7.07 (dq, ^3J = 7.5 Hz, J = 1.0 Hz, 2 H, *CH*, ar), 7.01 (dt, ^3J = 7.5 Hz, J = 1.0 Hz, 1 H, *CH*, ar), 4.63 (t, ^3J = 7.5 Hz, 1 H, 9-Flu *H*), 3.22 (d, ^3J = 7.5 Hz, 2 H, C H_2); ^{13}C{^{1}H} NMR (125.8 MHz, $CDCl_3$) δ 160.3, 150.0, 147.5, 141.2, 136.6, 127.5, 127.1, 125.1, 124.8, 122.1, 120.2, 47.6, 43.0; ^{15}N NMR (50.69 MHz, $CDCl_3$) δ −68.4; HRMS calcd for $C_{19}H_{15}N$ 257.1205, found 257.12060.

9-(3-Phenyl-propyl)-9*H*-fluorene (4d). In a 1-L 2-necked round-bottomed flask was suspended fluorene (**1**) (250 g, 1.50 mol) in 3-phenyl-1-propanol (**2d**) (450 mL, 3.30 mol) and 3-phenylpropionaldehyde (**3d**) (39 g, 0.29 mol). KOH pellets (120 g, 2.14 mol) were added, and the mixture was stirred at 185 °C for 4 h. During the reaction the mixture changed its colour from yellow to orange, red, and brown and turned yellow in the end again. The stirred reaction mixture was cooled to ambient temperature and neutralized with concentrated HCl. Toluene (1 L) and water (1 L) were added, and the organic phase separated, washed with water (1 × 1 L) and dried over $MgSO_4$. After removal of the volatiles at 50 °C in vacuo, methanol (500 mL, technical grade) was added to the warm oily product. The solution was cooled to 4 °C under stirring, and after 10 min crystallisation of product started. The suspension was stirred for additional 1 h at that temperature, and then the product was separated via filtration with suction (glass frit G3), washed with ice-cold MeOH (3 × 200 mL), and dried at 50 °C in vacuo to afford the title compound **4d** (389 g, 91%) as off white crystals. Purity (GC/NMR): >99%. ^{1}H and ^{13}C NMR spectra were identical to those in the literature.[28]

9-Butylidene-9*H*-fluorene (5). In a 2-L 3-necked round-bottomed flask were suspended fluorene (**1**) (166 g, 1.0 mol) and KO*t*Bu (119 g, 1.06 mol) in xylene (1.5 L) under an argon atmosphere. The reaction mixture was refluxed for 5 min under stirring. The formed orange suspension was cooled to 25 °C, and under stirring *n*-butyraldehyde (**3e**) (300 mL, 3.33 mol) was added dropwise during 5 min. The colour changed to greenish. The reaction mixture was refluxed for 5 min again, cooled to 25 °C, and neutralized with concentrated HCl. The reaction mixture was transferred into a separation funnel and washed with water (1 × 1 L). The organic layer was dried over $MgSO_4$, and the volatiles of the clear colourless filtrate were removed at 80 °C in vacuo to afford a slightly yellowish oil. Methanol (70 mL) was added to the oily crude product, and the solution was stirred at 0 °C. After some minutes the title compound crystallized, and the suspension was stirred for an additional 1 h at 0 °C. The product is separated via suction filtration (glass frit G3) and dried in vacuo (the product melts at 50 °C) to afford **5** (138 g, 63%) as a white solid. Purity (GC/NMR): >99%. HRMS calcd for $C_{17}H_{16}$ 220.1252, found 220.12700. ^{1}H and ^{13}C NMR spectra were identical to those the literature.[29]

9-Butyl-9*H*-fluorene (6). 9-Butylidene-9*H*-fluorene (**5**) (80 g, 0.136 mmol) was dissolved in EtOAc (120 mL, technical grade). Five percent Pd on carbon (2.0 g) was added, and the mixture was hydrogenated at 20–25 °C (external cooling with ice), 2 bar H_2 for 1.5 h. The catalyst was filtered off via celite, and the filtrate was evaporated at 50 °C in vacuo to afford **6** (80 g, 100%) as a clear colorless oil that solidified at room temperature. Purity (GC/NMR): >99%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (dq, ^3J = 7.5 Hz, J = 1.0 Hz, 2 H, *CH*, ar), 7.49 (ddt, ^3J = 7.5 Hz, J = 2.0 Hz, J = 1.0 Hz, 2 H, *CH*, ar), 7.34 (tddd, ^3J = 7.5 Hz, J = 1.0 Hz, J = 1.0 Hz, J = 1.0 Hz, 2 H, *CH*, ar), 7.28 (td, ^3J = 7.5 Hz, J = 1.0 Hz, 2 H, *CH*, ar), 3.96 (t, ^3J = 6.0 Hz, 1 H, 9-Flu *H*), 2.02–1.96 (m, 2 H, CH_2), 1.31–1.23 (m, 2 H, CH_2), 1.19–1.12 (m, 2 H, CH_2), 0.82 (t, ^3J

(28) Licht, E. H.; Alt, H. G.; Karim, M. M. *J. Organomet. Chem.* **2000**, *599*, 275.

(29) Malladi, R. R.; Kabalka, G. W. *J. Chem. Res. Synop.* **2002**, *5*, 224.

= 7.5 Hz, 3 H, CH_3); $^{13}C\{^1H\}$ NMR (125.8 MHz, $CDCl_3$) δ 148.1, 141.6, 127.3, 127.2, 124.8, 120.2, 47.9, 33.2, 28.2, 23.4, 14.3; HRMS calcd for $C_{17}H_{18}$ 222.1408, found 222.13953.

BnFluPCy$_2$·HBF$_4$ (8a). In a 6-L 3-necked round-bottomed flask was suspended 9-benzyl-9*H*-fluorene (**4a**) (90 g, 0.351 mol) in dry MTBE (3 L) under an argon atmosphere. At 0 °C *n*-BuLi (2.5 M in hexane, 139 mL, 0.348 mol) was added within 10 min. The reaction mixture was allowed to warm to 20 °C, a deep red, clear solution formed, and stirring was continued for an additional 2 h at ambient temperature. Then the mixture was cooled to −30 °C, and Cy_2PCl (**7**) (79.05 g, 0.340 mol) was added within 10 min. The red colour disappeared to form a yellow clear solution, which was stirred for an additional 1 h at 20 °C (after about 20 min precipitation of LiCl started). The suspension was extracted with degassed water (1 × 750 mL) to remove the LiCl. The clear, slightly yellowish organic layer was treated with aqueous HBF_4 (48%, 50.5 mL, 0.386 mol) under vigorous stirring within 2 min to precipitate the title compound as white crystals. Additional HBF_4 (2 M in water, 25 mL) was added, and the suspension was stirred for another 10 min. Product was separated via suction filtration (glass frit G3), washed with MTBE (2 × 100 mL), and dried at 60 °C in vacuo to afford **8a** (180 g, 98%) as white crystals. ^1H, ^{13}C, and ^{31}P NMR spectra were identical with the literature.[14]

PhenPropFluPCy$_2$·HBF$_4$ (8b). In a 6 L 3 necked round bottomed flask 9-(3-phenyl-propyl)-9H-fluorene (**4d**) (117 g, 0.410 mol) were suspended in dry MTBE (2.7 L) under an argon atmosphere. At 0 °C n-BuLi (2.5 M in hexane, 162 mL, 0.406 mol) were added within 10 min. The reaction mixture was warmed to 20 °C forming a deep red, clear solution which was stirred for additional 2 h at ambient temperature. Then the mixture was cooled to −30 °C, and Cy_2PCl (**7**) (92.75 g, 0.399 mol) was added within 10 min. The red colour disappeared to form a yellow clear solution, which was stirred for an additional 1 h at 20 °C (after about 20 min precipitation of LiCl started). The suspension was extracted with degassed water (1 × 750 mL) to remove the LiCl. The clear, slightly yellowish organic layer was treated with aqueous HBF_4 (48%, 59 mL, 0.451 mol) under vigorous stirring within 2 min to precipitate the title compound as white crystals. Additional HBF_4 (2 M in water, 25 mL) was added, the suspension stirred for another 10 min, and the precipitate was separated via suction filtration (glass frit G3) and washed with MTBE (2 × 100 mL). Drying of the product at 60 °C in vacuo afforded **8b** (208 g, 92%) as white crystals. ^1H, ^{13}C, and ^{31}P NMR spectra were identical to those the literature.[14]

BuFluPCy$_2$·HBF$_4$ (8c). In a 6-L 3-necked round-bottomed flask was suspended 9-butyl-9*H*-fluorene (**6**) (113.7 g, 0.511 mol) in dry MTBE (3.2 L) under an argon atmosphere. At 0 °C *n*-BuLi (2.5 M in hexane, 200 mL, 0.500 mol) was added within 15 min. The reaction mixture was warmed to 20 °C and formed a deep red, clear solution, which was stirred for an additional 2 h at ambient temperature. Then the mixture was cooled to −30 °C again, and Cy_2PCl (**7**) (113.8 g, 0.489 mol) was added within 15 min. The red colour disappeared to form a yellow clear solution, which was stirred for an additional 1 h at 20 °C (after about 20 min precipitation of LiCl started). The suspension was extracted with degassed water (1 × 750 mL) to remove the LiCl. The clear, slightly yellowish organic layer was treated with aqueous HBF_4 (48%, 67 mL, 0.511 mol) under vigorous stirring within 2 min to precipitate the title compound as white crystals. Additional HBF_4 (2 M in water, 25 mL) was added, the suspension was stirred for another 10 min, and the precipitate was separated via suction filtration (glass frit G3) and washed with MTBE (2 × 100 mL). Removal of the volatiles at 60 °C in vacuo afforded **8c** (234 g, 95%) as white crystals. ^1H NMR (500 MHz, $CDCl_3$) δ 7.89 (dd, ^3J = 7.5 Hz, J = 0.5 Hz, 2 H, ar), 7.80 (d, ^3J = 7.5 Hz, 2 H, ar), 7.59 (tt, ^3J = 7.5 Hz, J = 1.3 Hz, 2 H, ar), 7.53 (td, ^3J = 7.5 Hz, J = 1.3 Hz, 2 H, ar), 6.51 (dt, ^1J = 479.52 Hz, J = 2.5 Hz, 1 H, P*H*), 2.70–2.64 (m, 2 H, CH_2 (butyl)), 2.23 (qq, J = 12.3 Hz, J = 2.7 Hz, 2 H, CH_2), 1.93–1.85 (m, 2 H, C*H*), 1.80–1.48 (m, 8 H, CH_2), 1.40 (qdd, J = 12.6 Hz, J = 4.5 Hz, J = 3.7 Hz, 2 H, CH_2), 1.27–1.06 (m, 10 H, CH_2), 0.66 (t, ^3J = 7.3 Hz, 3 H, CH_3), 0.59–0.51 (m, 12 H, CH_2 (butyl)); $^{13}C\{^1H\}$ NMR (125.75 MHz, $CDCl_3$) δ 141.8 (d, J_{PC} = 4.4 Hz), 140.5 (d, J_{PC} = 1.5 Hz), 130.6, 129.5, 125.4 (d, J_{PC} = 2.9 Hz), 121.5, 52.8 (d, J_{PC} = 32.2 Hz), 34.0, 31.6 (d, J_{PC} = 36.0 Hz), 29.8 (d, J_{PC} = 3.4 Hz), 28.4 (d, J_{PC} = 3.5 Hz), 27.1 (d, J_{PC} = 13.2 Hz), 26.9 (d, J_{PC} = 12.8 Hz), 25.3, 24.8 (d, J_{PC} = 9.9 Hz), 22.6, 14.0; $^{31}P\{^1H\}$ NMR (202.45 MHz, $CDCl_3$) δ 35.3; ^{31}P NMR (202.45 MHz, $CDCl_3$) δ 35.3 (d, ^{PH}J = 479 Hz).

Acknowledgment

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Supporting Information Available

NMR spectra (^1H, ^{13}C, ^{15}N, ^{31}P) of the previously unknown compounds. This information is available free of charge via the Internet at http://pubs.acs.org.

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OP7001479

4.4. Effiziente Suzuki-Kupplung N-heterocyclischer Substrate in reinem Wasser als Lösemittel

Der Inhalt dieses Kapitels wurde bereits veröffentlicht:

Christoph A. Fleckenstein, Herbert Plenio, "*Aqueous Cross Coupling: Highly Efficient Suzuki-Miyaura of N-Heteroaryl Halides and N-Heteroarylboronic Acids*", *Green Chem.* **2007**, *9*, 12, 1287-1291.

Die in Kapitel 4.1. beschriebenen Palladiumkomplexe mit dem monosulfonierten Phosphin EtFluPCy$_2$ ermöglichten bereits effiziente Suzuki-Kupplungen verschiedenster Substrate in reinem Wasser. Die Wasserlöslichkeit dieser Pd-Komplexe ist jedoch recht begrenzt. Die Erhöhung der Polarität und damit einhergehend der Löslichkeit war durch Einführung einer zweiten Sulfonsäuregruppe in die Ligandenstruktur erreichbar. Eine direkte Doppelsulfonierung des aktiven EtFluPCy$_2$-Liganden war aus Gründen der Deaktivierung des aromatischen Systems nach der Erstsulfonierung unter den benötigten milden Bedingungen *nicht* möglich. Versuche zur Doppelsulfonierung von EtFluPCy$_2$ unter drastischeren Bedingungen ermöglichten lediglich die Isolation von P(V)-Spezies. Die Einführung der zweiten Sulfonsäuregruppe in einen Liganden der Fluorenyldialkylphosphinklasse gelingt einfach, quantitativ und selektiv mittels Sulfonierung des in Abbildung 67 gezeigten Phosphoniumtetrafluoroborats. Dieses weist zwei voneinander elektronisch unabhängige, jeweils einfach sulfonierbare, aromatische Systeme auf.

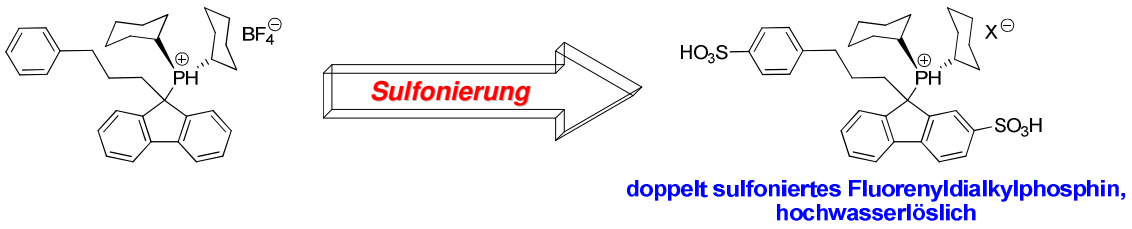

Abbildung 67. Ein doppelt sulfonierter Vertreter der Fluorenyldialkylphosphinklasse.

Pd-Komplexe mit diesem doppelt sulfonierten Phosphin (***cataCXium® FSulf***) ermöglichen effiziente Suzuki-Kreuzkupplungen diverser *N*-Heteroarylchloride mit verschiedenen Phenyl- und Naphthylboronsäuren in reinem Wasser. Quantitativer Umsatz ist in diesen Fällen mit Katalysatorbeladungen von 0.02-0.05 mol% zu erreichen, Heteroboronsäuren lassen sich mit 0.1-0.5 mol% des wasserlöslichen Katalysators quantitativ kuppeln.

Bei Synthesen im Multigramm-Maßstab wird ein interessanter Vorteil offensichtlich: Aufgrund der Schwerlöslichkeit der Produkte im wässrigen Reaktionsmedium scheiden sich diese am Ende der Reaktion als organische Phase ab. Dieser Umstand ermöglicht eine einfache physikalische Produktabscheidung ohne den im Allgemeinen üblichen Zusatz weiterer organischer Lösemittel. Der wasserlösliche Katalysator, in der Reaktion benötigte Reagenzien, überschüssige Boronsäure sowie anfallende anorganische Nebenprodukte bleiben in der Wasserphase gelöst. Die gebildeten Produkte lassen sich in >90 % Ausbeute und >98 % Reinheit ohne weiteren Aufreinigungsschritt isolieren.

Milde Reaktionstemperaturen (100 °C), Kaliumcarbonat als preiswerte und nichttoxische Base sowie die Möglichkeit der Produktabtrennung ohne Zusatz organischer Lösemittel bei Katalysen in größerem Maßstab lassen das entwickelte Verfahren in besonderem Maße nachhaltig erscheinen.

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Aqueous cross-coupling: highly efficient Suzuki–Miyaura coupling of *N*-heteroaryl halides and *N*-heteroarylboronic acids†

Christoph A. Fleckenstein and Herbert Plenio*

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The palladium complex of the new disulfonated 9-(3-phenylpropyl)-9′-PCy$_2$-fluorene ligand is a highly active catalyst for aqueous Suzuki coupling reactions of *N*-heterocyclic chlorides and *N*-heterocyclic boronic acids; catalyst loadings of 0.02–0.1 mol% of Pd and two equiv. of phosphine result in the near quantitative formation of the respective coupling products at 100 °C.

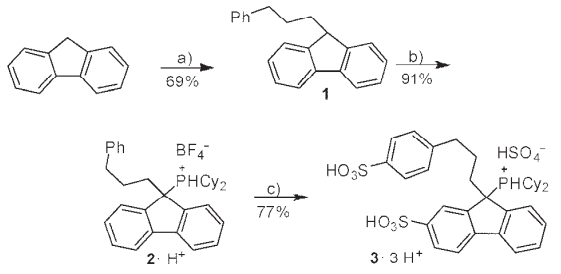
During the last decade the Suzuki–Miyaura coupling reaction has become a powerful tool in synthetic chemistry.[1] However, most of the catalysts used for such reactions were developed to perform best in organic solvents. The use of water is primarily discussed in the context of green solvents[2] but less so as a solvent leading to the superior performance of the catalyst.[3,4] According to a recent MDL Drug Data Report, pyridines are the most common heterocycles in pharmaceutically active compounds.[5] Unfortunately, nitrogen-containing heterocycles are difficult substrates for Suzuki coupling reactions.[6–9] Especially, electron-rich pyridines with amino-substituents *ortho*- or *para*- to the pyridine nitrogen atom display high basicities which go along with an increasing propensity for the coordination (inhibition) of the catalytically active palladium complexes. Improvements in the coupling of such substrates were recently reported by Guram *et al.*,[10] Buchwald and co-workers[11] and Fu's group.[12] Interestingly, coupling reactions involving such substrates were performed in water or water containing solvent mixtures (with toluene, dioxane, CH_3CN or butanol). We reasoned that, in the presence of water, the nitrogen atoms prefer to engage in hydrogen bonding with water rather than to coordinate to the soft Pd, leading to much higher catalytic activities. However, all of the catalysts previously employed were not optimized for use in water with respect to solubility.

Consequently, we attempted the synthesis of highly water-soluble ligands to enable Pd-catalyzed coupling reactions in pure water as the solvent at low catalyst loading.

We recently reported the synthesis of fluorenyldialkylphosphines whose Pd complexes are excellent catalysts for various cross-coupling reactions.[13,14] The facile introduction of functional groups was demonstrated with the monosulfonation of a 9-ethyl-fluoren-9-yl-dicyclohexylphosphine, but the solubility of the respective Pd complexes in water is modest. Consequently, we wish to describe here the synthesis of a disulfonated fluorenyl-dicyclohexylphosphine and the preliminary screening of the catalytic activity of the respective Pd complexes in the Suzuki cross-coupling of various *N*-heterocyclic substrates. Furthermore, the use of the solvent water leads to catalysts which are superior to the best ones used in conventional organic solvents. In this manner, optimum catalytic performance and benign properties are combined.

In order to obtain a disulfonated fluorenylphosphine the use of more reactive sulfonating reagents (oleum, $ClSO_3H$) on 9-ethyl-fluoren-9-yl-dicyclohexylphosphine was tested, but led to the oxidation of the P(III) centre during aqueous workup. Less forcing reaction conditions gave the monosulfonated product. Consequently, we decided to introduce another phenyl ring in the periphery of the ligand to serve as an anchor for the second sulfonato group. First the 9-fluorenyl anion was reacted with 1-bromo-3-phenylpropane to result in the 9-alkylfluorene **1** (Scheme 1); deprotonation of **1** with *n*BuLi and reaction with Cy_2PCl led to the formation of the fluorenylphosphine **2**, whose treatment with sulfuric acid leads to the double sulfonation. Starting from fluorene, the disulfonated fluorenylphosphine **3** is easily available in three steps in a 49% overall yield, making use of simple, commercially available starting materials.

We have tested a number of different 2-chloropyridines and 2-chloroquinolines in Suzuki reactions of various boronic acids (mainly tolyl-, naphthyl-boronic acids, Table 1, entries 1–20). The catalyst is formed *in situ* from Na_2PdCl_4, and two equivalents of the triply protonated ligand **3** in the presence of five equivalents of base. Under these reaction conditions all substrates are converted in quantitative yields into the respective products. No conversion at all was observed in the absence of the phosphine ligand. Typical coupling reactions were carried out at 100 °C in pure water during 12 h with K_2CO_3 as the base utilizing between 0.02 and 0.05 mol% of Pd catalyst. Notably, even difficult substrate combinations, such as the highly basic 2-chloro-4-aminopyridine with tolylboronic



Scheme 1 Synthesis of double sulfonated fluorenyldicyclohexylphosphine. *Reagents and conditions*: a) *n*BuLi, 1-bromo-3-phenylpropane, THF, −60 °C; b) *n*BuLi, Cy_2PCl, Et_2O, −60 °C, $HBF_4{\cdot}Et_2O$; c) CH_2Cl_2, H_2SO_4, 50 °C.

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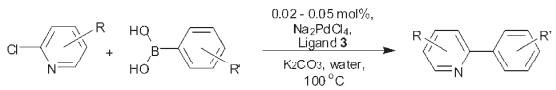
† Electronic supplementary information (ESI) available: Spectra of the new coupling products. See DOI: 10.1039/b711965h

Table 1 Suzuki reaction with *N*-heteroaryl chlorides in water[a]



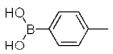
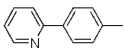
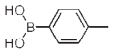
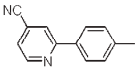
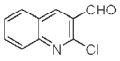
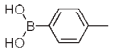
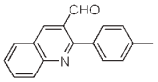
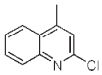
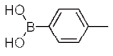
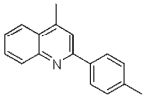
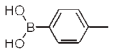
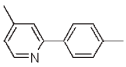
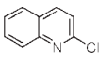
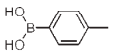
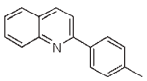
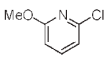
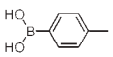
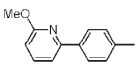
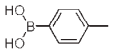
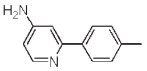
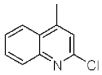
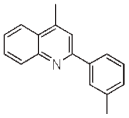
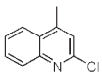
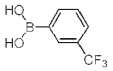
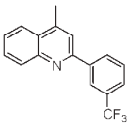
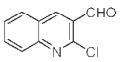
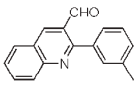
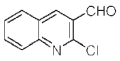
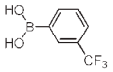
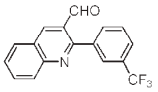
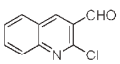
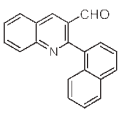
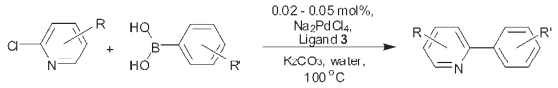
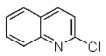
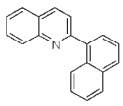
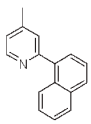
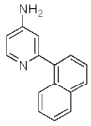
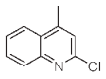
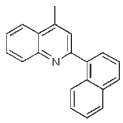
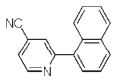
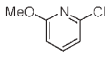
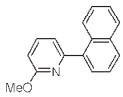
Entry	Aryl chloride	Boronic acid	Product	Yield (%)[b]
1				≥99[c] 95
2				≥99[c] 93
3				≥99[c] 97
4				≥99[d] 95
5				≥99[d] 92
6				≥99[c] 95
7				≥99[d] 94
8				≥99[d] 92
9				≥99[d] 96
10				≥99[d] 95
11				≥99[c] 93
12				≥99[c] 92
13				≥99[d] 96
14				≥99[d] 94

Table 1 Suzuki reaction with *N*-heteroaryl chlorides in water[a] (*Continued*)



Entry	Aryl chloride	Boronic acid	Product	Yield (%)[b]
15				≥99[d] 95
16				≥99[d] 93
17				97[d] 90
18				≥99[d] 95
19				≥99[d] 94
20				≥99[d] 98

[a] Reaction conditions: 1.0 equiv. aryl halide, 1.2 equiv. boronic acid, 3.2 equiv. K_2CO_3, degassed water (4 mL mmol^{-1}), 100 °C, 12 h, cat. (respective volume of catalyst stock solution, c_{Pd} = 0.01 mol L^{-1}, Na_2PdCl_4/ligand **3**·3H$^+$, L/Pd = 2 : 1). Reaction times not optimized. [b] Average of two runs; the first number indicates the conversion determined *via* GC using an internal heptadecane standard, the second number is the isolated yield (column chromatography). [c] [Pd] = 0.02 mol%. [d] [Pd] = 0.05 mol%.

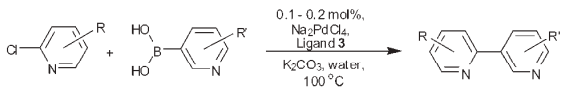
acid or the sterically hindered naphthylboronic acid (entries 13–20) require only 0.05 mol% of catalyst for quantitative conversion at 100 °C; 3-CF_3-substituted phenylboronic acid, as an example for an electron-deficient metalloid (entries 10 and 12), is quantitatively reacted at 0.02–0.05 mol%.

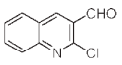
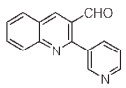
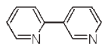
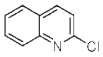
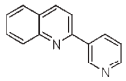
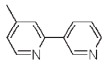
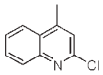
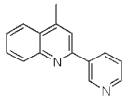
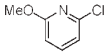
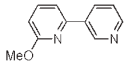
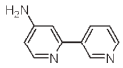
Even more difficult coupling reactions are those in which both coupling partners contain nitrogen donors. We tested several reactions of 2-chloropyridines and 2-chloroquinolines with 3-pyridineboronic acid (Table 2) using 0.1 mol% catalyst leading to the quantitative formation of the respective coupling products (entries 1–5). Suzuki–Miyaura reactions of the more electron-rich methoxy-substituted 2-chloropyridine (entry 6) gives 93% conversion and 90% isolated yield. The most challenging combination is that of 2-chloro-4-aminopyridine and 3-pyridineboronic acid (entry 7), which gives 94% conversion at 0.2 mol% catalyst. Consequently, the present catalyst is 10–100 times more active than other systems, which typically require 1–2 mol% Pd at slightly higher temperatures (100–120 °C).[10,11,15] To the best of our knowledge, the catalysts reported here are the most efficient for the Suzuki–Miyaura coupling with chloropyridines.[11,12,16–24]

All products from the screening experiments were obtained by ether extraction from the aqueous solution. In order to demonstrate that organic solvents can be completely avoided in the synthesis of the coupling products, we have run one coupling reaction [2-chloro-4-picoline + $PhB(OH)_2$] on a gram-scale. After the coupling reaction, the water-insoluble product deposits as an oil on the water surface, which can be separated easily from the aqueous phase containing base and excess boronic acid. The purity of the crude product is excellent (>98%).

In conclusion, a disulfonated sterically demanding and electron-rich fluorenylphosphine was synthesized in three steps from simple, commercially available starting materials in 49% overall yield. We have demonstrated for numerous substrate combinations that chloropyridines (quinolines) and aryl- or pyridineboronic acids can be Suzuki coupled in quantitative yields in pure water as the solvent, typically using between 0.02 and 0.1 mol% of Pd catalyst at 100 °C. We are currently evaluating the potential of this catalyst system in aqueous Sonogashira and Buchwald–Hartwig cross-coupling reactions also using different substitution patterns.

Table 2 Suzuki reaction with *N*-heteroaryl chlorides and *N*-heteroarylboronic acids in water[a]



Entry	Aryl chloride	Boronic acid	Product	Yield (%)[b]
1				≥99[c] 95
2				≥99[c] 96
3				≥99[c] 93
4				≥99[c] 92
5				≥99[c] 95
6				93[c] 90
7				94[d] 90

[a] Reaction conditions: 1.0 equiv. aryl halide, 1.2 equiv. boronic acid, 3.2 equiv. K_2CO_3, degassed water (4 mL mmol^{-1}), 100 °C, 12 h, cat. (respective volume of catalyst stock solution, c_{Pd} = 0.01 mol L^{-1}, Na_2PdCl_4/ligand **3**·3H$^+$, L/Pd = 2 : 1). Reaction times not optimized. [b] Average of two runs: the first number indicates the conversion determined *via* GC using an internal heptadecane standard, the second number is the isolated yield (column chromatography). [c] [Pd] = 0.1 mol%. [d] [Pd] = 0.2 mol%.

Experimental. *Catalyst stock solution*: Na_2PdCl_4 (5.9 mg, 0.02 mmol), phosphonium salt (**3**·3 H$^+$) (50 mg) and K_2CO_3 (300 mg) were placed in Schlenk tube. Water (20 mL) was added and the mixture was stirred at 50–55 °C for 2 h until the clear solution turns nearly colourless. This stock solution has a concentration of c_{Pd} = 0.001 mol L^{-1}. *Cross-coupling reaction*: to the aryl chloride (1 mmol), boronic acid (1.5 mmol) and K_2CO_3 (2 mmol), water (4 mL) and the catalyst stock solution were added. The reaction mixture was stirred at 100 °C in an aluminium block during 12 h. After cooling to room temperature the reaction mixture was diluted with diethyl ether (15 mL), washed with water (10 mL), the organic phase dried over $MgSO_4$, filtered and concentrated *in vacuo*. Products were purified by column chromatography. Alternatively the yield was determined *via* gas chromatography with heptadecane or diethylene glycol di-*n*butyl ether as an internal standard.

Procedure for gram-scale cross-coupling reaction. Preparation of the catalyst solution: Na_2PdCl_4 (11.8 mg, 0.04 mmol), phosphonium salt (**3**·3H$^+$) (100 mg) and K_2CO_3 (500 mg) were placed in Schlenk tube. Water (25.0 mL) was added and the mixture was stirred at 55 °C for 2 h until the clear solution turns nearly colourless. *Cross-coupling reaction*: a 30 mL Schlenk tube was charged with phenylboronic acid (3.17 g, 26 mmol) and K_2CO_3 (5.53 g, 40 mmol). The reaction vessel was evacuated and backfilled with argon twice. The catalyst solution and 2-chloro-4-picoline (1.75 mL, 20 mmol) were added. The reaction mixture was stirred vigorously for 12 h at 100 °C and then allowed to cool down to ambient temperature without stirring. A brown organic (upper) oily layer separates and was transferred into a flask. This oil was vacuum stripped at 40 mbar at 80 °C for 1 h to afford 3.05 g (90%) of the crude product as a brown oil. Purity >98% (GC-FID, ^{1}H-NMR).

This work was supported by the DFG and the Degussa AG, Provadis (Partner für Bildung und Beratung) GmbH, C. A. F. by the Fonds der Chemischen Industrie and the Studienstiftung des Deutschen Volkes with a fellowship. Experimental support by Jan Pschierer is acknowledged.

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4.5. Hocheffiziente Suzuki-Kupplung N-heterocyclischer Substrate durch rationales Reaktionsdesign

Der Inhalt dieses Kapitels wurde bereits veröffentlicht:

Christoph A. Fleckenstein, Herbert Plenio, *"Highly Efficient Suzuki-Miyaura Coupling of Heterocyclic Substrates through Rational Reaction Design"*, *Chem. Eur. J.* **2008**, *14*, 4267-4279.

Die Kupplung *N*-Donor-haltiger Substrate (z.B. *N*-heterocyclische Arylchloride, *N*-heterocyclische Boronsäuren, Substrate mit ungeschützten Aminofunktionalitäten) bereitet in Pd-vermittelten Katalysen oft Probleme. Kompetitive Komplexierung durch die Substrate führt häufig zu einer Deaktivierung des Katalysatorkomplexes. Im vorangegangenen Kapitel konnte gezeigt werden, dass der Einsatz von Wasser als Lösemittel in Verbindung mit dem hochwasserlöslichen Pd-*cataCXium® FSulf*-Komplex bislang beispiellose katalytische Aktivität bei der Suzuki-Kupplung dieser „Problemsubstrate" ermöglicht. Dies lässt sich darauf zurückführen, dass die Stickstoffdonoren durch Ausbildung von Wasserstoffbrückenbindungen mit Wasser nicht mehr als kompetitive Liganden für das Katalysemetall zur Verfügung stehen.

Eine Barriere, die zur weiteren Steigerung der Katalyseaktivität zu überwinden ist, stellt die schlechte Löslichkeit der weitgehend unpolaren Substrate und Produkte in Wasser dar. In diesem Kapitel wird die Steigerung der katalytischen Aktivität durch rationale Optimierung der Reaktionsbedingungen beschrieben.

Die Verwendung von *n*-Butanol als Cosolvens und anschließende Optimierung des Mischungsverhältnisses von *n*-Butanol/Wasser-Mischungen als Reaktionsmedium hat eine signifikante Aktivitätssteigerung des katalytischen Systems zur Folge, ohne dass die Vorteile des wässrigen Systems wie Nachhaltigkeit oder Praktikabilität des Verfahrens verloren gehen. Das als optimal gefundene *n*-Butanol/Wasser-Verhältnis von 3:1 ermöglicht die homogene, einphasige Kupplung unter Reaktionsbedingungen (100 °C) und eine anschließende leichte Produktisolation aufgrund der Entmischung der wässrigen und der organischen Phase bei Raumtemperatur.

Die Robustheit des entwickelten Reaktionsprotokolls wird durch erfolgreiche Kupplung unterschiedlicher *N*- oder *S*-heterocyclischer Substrattypen demonstriert. Die benötigten

Katalysatorkonzentrationen zur Erreichung eines quantitativen Umsatzes liegen zwischen 0.005 und 0.5 mol%. Erfolgreich umgesetzte Substratklassen sind:

- deaktivierte, nichtheterocyclische Chloraromaten
- Chlorpyridine
- Chlorchinoline
- Aromaten mit freien Aminofunktionalitäten
- Chlorpurine
- Chlorthiophene
- Chlorbenzothiazole
- Phenylboronsäuren
- Naphthylboronsäuren
- Pyridinboronsäuren
- Indolboronsäuren

FULL PAPER

DOI: 10.1002/chem.200701877

Highly Efficient Suzuki–Miyaura Coupling of Heterocyclic Substrates through Rational Reaction Design

Christoph A. Fleckenstein and Herbert Plenio*[a]

Abstract: A dicyclohexyl(2-sulfo-9-(3-(4-sulfophenyl)propyl)-9*H*-fluoren-9-yl)phosphonium salt was synthesized in 64% overall yield in three steps from simple commercially available starting materials. The highly water-soluble catalyst obtained from the corresponding phosphine and $[Na_2PdCl_4]$ enabled the Suzuki coupling of a broad variety of *N*- and *S*-heterocyclic substrates. Chloropyridines (-quinolines) and aryl chlorides were coupled with aryl-, pyridine- or indoleboronic acids in quantitative yields in water/*n*-butanol solvent mixtures in the presence of 0.005–0.05 mol% of Pd catalyst at 100°C, chloropurines were quantitatively Suzuki coupled in the presence of 0.5 mol% of catalyst, and *S*-heterocyclic aryl chlorides and aryl- or 3-pyridylboronic acids required 0.01–0.05 mol% Pd catalyst for full conversion. The key to the high activity of the Pd-phosphine catalyst is the rational design of the reaction parameters (i.e., the presence of water in the reaction mixture, good solubility of reactants and catalyst in *n*-butanol/water (3:1), and the electron-rich and sterically demanding nature of the phosphine ligand).

Keywords: cross-coupling · indoles · palladium · purines · thiophenes

Introduction

The biological activity associated with numerous nitrogen- and sulfur-containing heterocycles explains their wide use as active pharmaceutical ingredients.[1–6] Consequently, a sizable portion of recent US patents reports on organic process development of aromatic heterocycles.[7,8] A useful synthetic tool for the modification of such compounds is the Suzuki–Miyaura coupling,[9,10] which has been applied for the preparation of arylpyridines,[11,12] bipyridines,[11–15] arylpyrimidines,[16–18] pyridopyridines[11,12,19–21] and aryltriazines,[22,23] the synthesis of nucleosides[24,25] or the introduction of thiophene,[26,27] benzothiazole[28] or indolyl[29–32] moieties.

Nonetheless, the cross-coupling chemistry of heterocyclic substrates suffers from limitations. In particular, *N*-heterocycles or compounds bearing free amino moieties are regarded as challenging substrates.[11,33–37] Problems include the inhibition of the catalytically active centre by *N*-coordination, the trimerization of boronic acids[38] and the poor reactivities of electron-deficient boronic acids. In some cases primary or secondary amino groups have been masked by protective groups to allow the coupling of such substrates, while without *N*-protection the Suzuki coupling was less efficient.[39] Lacking general and efficient cross-coupling protocols, synthetic chemists resort to heteroaryl bromides as coupling substrates[40,41] instead of the cheaper and more easily available aryl chlorides, which require at least 1 mol% of catalyst for quantitative conversion.[42–44] Recently, significant improvements in the coupling of heteroaryl chlorides have been reported by Guram et al.,[45,46] Buchwald et al.[35] and Fu et al.[33] Interestingly, some of the more efficient coupling reactions involving heterocyclic substrates were performed in water[25,47–60] or in water-containing solvent mixtures (with toluene, dioxane, CH_3CN or *n*-butanol).

We have recently demonstrated that water in combination with water-soluble, sulfonated fluorenylphosphine Pd complexes is a very useful solvent for Suzuki coupling reactions of *N*-heterocycles.[61] Our working hypothesis is that basic nitrogen atoms in pyridines, indoles or primary amines prefer to engage in hydrogen-bonding interactions with water rather than to inhibit the catalytically active metal centre. Apart from being a cheap, safe and benign solvent,[62–64] water has the additional advantage that the organic products of the coupling reactions are often poorly soluble and can thus easily be separated from the reaction mixture. This advantage, though, also turns out to be a drawback, as the aryl halide reactants tend to be poorly soluble in water, leading

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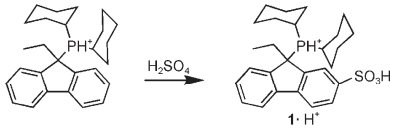
to a decrease in the overall rate of the coupling reaction due to mass transfer limitations. In order to improve the efficiency of Suzuki reactions further, we reasoned that increasing the solubility of the reactants in water by addition of a co-solvent should lead to even faster Suzuki coupling reactions. However, this must be achieved without compromising the previously mentioned advantages. The cosolvent should be benign: it should form a biphasic mixture with water at room temperature and a single solvent phase at elevated temperatures to avoid mass transfer limitations.[65] *n*-Butanol fulfils the criteria defined above: it has a large phase separation region with water at room temperature,[66] but forms monophasic mixtures at elevated temperatures, does not interfere with the Suzuki reaction, has a satisfactory boiling point and proves to represent a good trade-off between economical, safety and ecological aspects.[67,68]

We wish to report here on highly efficient Suzuki coupling reactions of various *N*- and *S*-heterocyclic substrates in the presence of a highly water-soluble catalyst, based on a disulfonated phosphine, in an optimized water/*n*-butanol mixture.

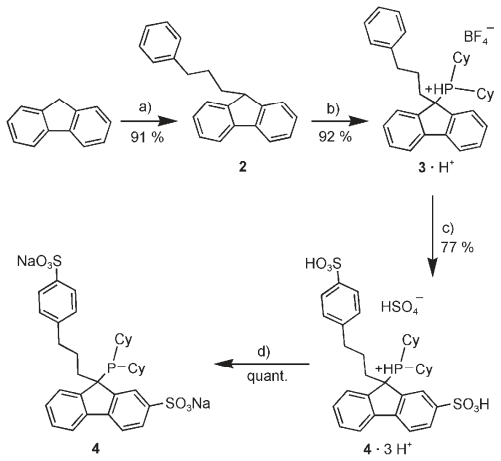
Results and Discussion

Synthesis of a highly water-soluble disulfonated fluorenyldialkylphosphine: We have recently reported the synthesis of fluorenylphosphines whose Pd complexes are excellent catalysts for various cross-coupling reactions.[61,69,70] Some of these phosphines are easily monosulfonated by treating their respective phosphonium salts with sulfuric acid (Scheme 1).[61] Nonetheless, the water solubilities of the corresponding Pd–phosphine complexes remain modest.



Scheme 1. Monosulfonation of a 9-ethylfluorenyldicyclohexylphosphonium salt.

Disulfonation of 9-ethylfluoren-9-yldicyclohexylphosphonium salt $\mathbf{1}\cdot H^+$ was not successful. The use of more reactive sulfonating reagents (oleum, $ClSO_3H$) on phosphine **1** led to the quantitative oxidation of P^{III} during aqueous workup, while less forcing reaction conditions afforded only the monosulfonated product. Consequently, we introduced another phenyl ring at the periphery of the ligand to serve as an anchor for a second sulfonato group (Scheme 2). The corresponding dicyclohexylfluorenylphosphonium salt **3** is readily sulfonated on treatment with sulfuric acid, affording the disulfonated fluorenylphosphonium salt $\mathbf{4}\cdot 3H^+$. Treatment of this reaction mixture with dilute NaOH and subsequent methanolic workup afforded the free phosphine **4** as the corresponding sodium salt in 65% overall yield from fluorene,



Scheme 2. Synthesis of the disulfonated fluorenyldialkylphosphine **4**. a) 3-phenylpropan-1-ol, 3-phenylpropanal, KOH, 150°C; b) *n*BuLi, Cy_2PCl, MTBE, −30°C, aq. HBF_4; c) CH_2Cl_2, H_2SO_4, 50°C; d) NaOH.

through the use of simple commercially available starting materials.[71] Following our report on the large-scale synthesis of various fluorenylphosphines (including $\mathbf{3}\cdot H^+$),[70] we now routinely perform the double sulfonation of $\mathbf{3}\cdot H^+$ on a 50 g scale using sulfuric acid, completely avoiding the formation of undesired phosphine oxides—even when the reaction is carried out in the presence of oxygen.

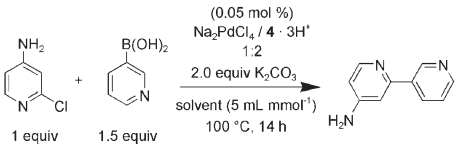
Optimizing the water/*n*-butanol system: As pointed out before, the poor solubility of aryl halides in pure water appears to be a drawback for coupling reactions in this solvent. We first wanted to test whether the addition of *n*-butanol as a co-solvent would enhance the catalytic activity of the [Pd/**4**] complex in Suzuki cross-coupling reactions. The catalyst was formed in situ by treatment of two equivalents of phosphonium salt $\mathbf{4}\cdot 3H^+$ with $[Na_2PdCl_4]$ in the presence of six equivalents of base and the reactants. We chose the coupling of 4-amino-2-chloropyridine and 3-pyridylboronic acid as the test reaction, and obtained quantitative conversion (93%) in water/*n*-butanol (1:1) solvent with the [Pd/**4**] complex as formed in situ as catalyst.

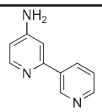
In pure water significantly lower conversion (44%) was observed under the same conditions (Table 1), while in *n*-butanol no coupling (<1%) occurred. This result confirms our initial idea that the reaction rate can be enhanced by providing better substrate solubility, while on the other hand a significant amount of water in the *n*-butanol is required to allow highly effective cross-coupling reactions.

We next studied the impact of the *n*-butanol/water ratio in Suzuki reactions of heterocycles to optimize the solvent composition in a more systematic manner. With the same catalyst as before, 2-chloro-4-picoline was coupled with *p*-tolylboronic acid in pure water, pure *n*-butanol or various mixtures of the two solvents (Figure 1).

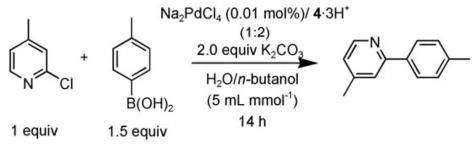
At 80°C and 0.01 mol% [Pd] loading in pure water 59% conversion was observed, increasing on addition of *n*-buta-

Table 1. Influence of solvent on catalytic activity: water versus water/*n*-butanol.



Entry	Aryl chloride	Boronic acid	Product	Conv. [%][a]
1				44[b] 93[c] <1[d]

[a] Average of two runs, determined by GC with heptadecane as internal standard. [b] In pure water as solvent. [c] In H_2O/*n*-butanol 1:1 as solvent. [d] In *n*-butanol.



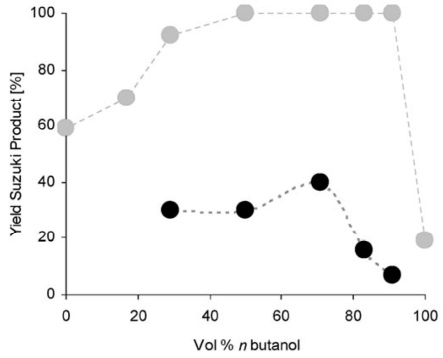


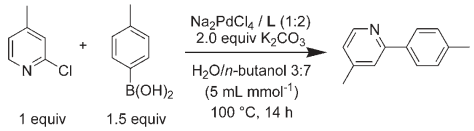
Figure 1. Effect of water/*n*-butanol ratio on catalytic activity. Reaction temperature: ●: 80 °C. ●: 60 °C.

nol to reach 100% conversion over a wide range of water/*n*-butanol compositions of 1:1 to 1:9. With a further increase in the alcohol content, the conversion drops drastically to only 19% conversion in pure *n*-butanol (technical grade). To identify the best solvent composition the screen was repeated at a lower reaction temperature (60 °C). Under these conditions a catalytic optimum was found at approximately 75% (*v*/*v*) *n*-butanol. Almost the same water/*n*-butanol composition was used by Billingsley and Buchwald for the Suzuki coupling of 2-bromothiophene and pyrrole boronate esters.[72]

From the water/*n*-butanol phase diagram,[66] we believe that a water/*n*-butanol 1:3 solvent mixture provides the highest possible water content in a homogeneous solution at 100 °C. At higher water contents the water/*n*-butanol mixture turns biphasic, leading to significantly diminished yields in cross-coupling reactions. Further increasing the amount of *n*-butanol results in drastically lowered yields—obviously a certain amount of water is very important. Consequently, the 1:3 water/*n*-butanol ratio represents a good trade-off between good substrate solubility, a monophasic reaction at elevated temperatures and biphasic behavior at ambient conditions, combined with maximum water content.

We next compared the catalytic activities of Pd complexes formed in situ with the doubly sulfonated phosphine **4**, the monosulfonated phosphine **1** and the phosphine **3**. Those three ligands are electron-rich and sterically demanding phosphines, which is essential for the formation of high-activity Pd complexes.[73,74] This was done to demonstrate the superiority of highly polar Pd complexes over their medium-polar and lipophilic counterparts. On treatment of 2-chloro-4-picoline with *p*-tolylboronic acid at 100 °C in the water/*n*-butanol (1:3) mixture, Pd complexes with the doubly sulfonated phosphine **4**·3H$^+$ showed significantly higher catalytic activity than their mono- and non-sulfonated relatives (Table 2). Under the same set of conditions, the palladium salt alone (i.e., in the absence of phosphine) does not afford any detectable cross-coupling product (Table 2, entry 3).

Table 2. Catalytic activity of water-soluble and water-insoluble catalysts.



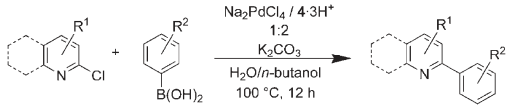
Entry	Ligand **L**	Cat. loading [mol%]	Yield [%][a]
1	**4**	0.01	>99
2	**4**	0.005	>99
3	–	0.01[b]	0
4	**1**	0.01	>99
5	**1**	0.005	73
6	**3**	0.01	79
7	**3**	0.005	59

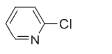
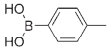
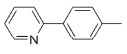
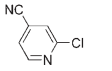
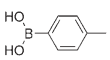
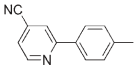
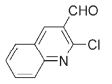
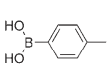
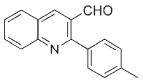
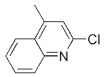
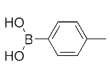
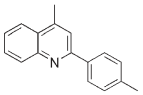
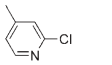
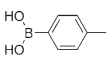
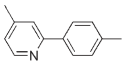
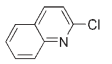
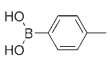
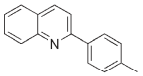
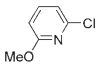
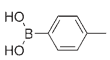
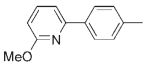
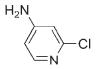
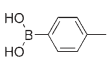
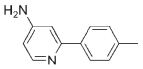
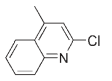
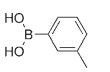
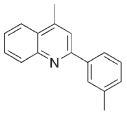
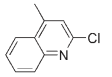
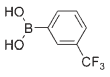
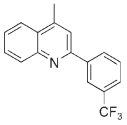
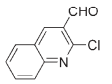
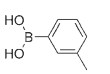
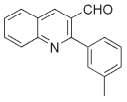
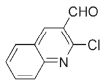
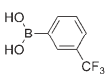
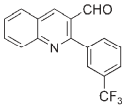
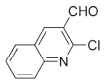
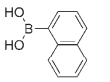
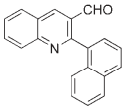
[a] Average of two runs, determined by GC with heptadecane as internal standard. [b] Control experiment: 0.01 mol% [Na_2PdCl_4], no phosphine ligand.

Suzuki cross-coupling of *N*-heterocycles: We next wanted to demonstrate the generality of the optimized reaction conditions for Suzuki reactions of *N*-heterocyclic substrates by coupling a number of different 2-chloropyridines and 2-chloroquinolines in Suzuki reactions with various boronic acids (mainly tolyl- and naphthylboronic acid) (Table 3).

Coupling reactions of 2-chloropyridines with sterically unhindered boronic acids (*p*-tolyl-, *m*-tolyl-) or electron-deficient *m*-(trifluoromethyl)phenylboronic acid were carried out at 100 °C in *n*-butanol/water (3:1) over 12 h with K_2CO_3 as the base and in the presence of 0.005 mol% of Pd catalyst[75] (Table 1, entries 1–12). Even with the sterically hindered 1-naphthylboronic acid, quantitative conversion was achieved in the presence of 0.01 mol% of Pd catalyst (Table 3, entries 13–19). Difficult substrates such as the highly basic 4-amino-2-chloropyridine reacted with *p*-tolyl-

Table 3. Suzuki reactions with 2-chloropyridines and 2-chloroquinolines with arylboronic acids in water/*n*-butanol (1:3)[a]



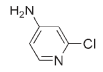
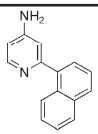
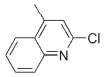
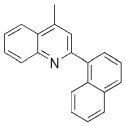
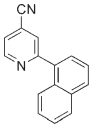
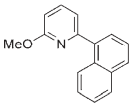
Entry	Aryl chloride	Boronic acid	Product	Pd [mol%]	Conv. [%][b]	Yield[c]
1				0.005	≥99	95
2				0.005	≥99	92
3				0.005	≥99	91
4				0.005	≥99	95
5				0.005	≥99	94
6				0.005	≥99	96
7				0.005	≥99	94
8				0.01 0.005	≥99 78	92
9				0.005	≥99	96
10				0.005	≥99	96
11				0.005	≥99	94
12				0.005	≥99	95
13				0.01	≥99	92
14				0.01	≥99	96
15				0.01	≥99	95

boronic acid or 1-naphthylboronic acid to afford quantitative conversions at 0.01 mol% catalyst loading (Table 3, entries 8, 16). For these substrates the Pd-phosphine complex **4** is about four times more active in water/*n*-butanol than in pure water and 10 to 100 times more active than other recently reported catalysts.[33,35,76]

Suzuki coupling of *N*-heterocyclic boronic acids: More challenging Suzuki substrate combinations are those in which both coupling partners contain a pyridyl or an amino moiety. In order to probe the activity of our catalytic system we screened reactions of various 2-chloropyridines and 2-chloroquinolines with 3-pyridylboronic acid. With 0.01 mol% catalyst loading, 2-chloropyridines and 2-chloroquinolines reacted smoothly with 3-pyridylboronic acid to afford near quantitative conversion (Table 4, entries 1–5). The highly basic 4-amino-2-chloropyridine was coupled in near quantitative yield with 3-pyridylboronic acid (Table 4, entry 7) or with 2,4-dimethoxy-3-pyridylboronic acid (Table 4, entry 9) when 0.05 mol% catalyst were applied.

Our optimized reaction protocol is not limited to 2-chloropyridines as coupling partners. Both 4-chloropyridine and the less activated 3-chloropyridine coupled quantitatively with *p*-tolylboronic acid (Table 5, entries 1 and 2) in the presence of as little as 0.05 mol% of catalyst. Sterically hindered boronic acids such as 2,6-dimethylboronic acid (Table 5, entry 3) reacted smoothly in the same manner with 4-chloropyridine. 3-Pyridylboronic acid—an electron-deficient metalloid—gave quantitative conversion with either 3-chloropyridine or 4-chloropyridine (Table 5, entries 4 and 5).

Table 3. (Continued)

Entry	Aryl chloride	Boronic acid	Product	Pd [mol%]	Conv. [%][b]	Yield[c]
16				0.01	≥99	91
17				0.01	≥99	94
18				0.01	≥99	91
19				0.01	≥99	95

[a] Reaction conditions: 1.0 equiv aryl halide, 1.2 equiv boronic acid, 3.2 equiv K_2CO_3, degassed water (1.5 mL mmol^{-1}), degassed *n*-butanol (4.5 mL mmol^{-1}), 100 °C, cat.: the corresponding volume of aqueous catalyst stock solution (c_{Pd} = 0.001 mol L^{-1}, Na_2PdCl_4/ligand (**4**·3H$^+$) L/Pd 2:1. Reaction times and temperature were not optimized. [b] Average of two runs, determined by GC with heptadecane as internal standard. [c] Average of two runs; products were isolated by column chromatography (silica gel), cyclohexene/EtOAc/NEt_3 10:1:1.

Application of the standard coupling protocol to deactivated 4-chloroanisole with the sterically hindered and electron-deficient 2,4-dimethoxy-3-pyridylboronic acid led to quantitative product formation (Table 4, entry 8). The same outcome was observed when the deactivated 1-(4-chlorophenyl)-1*H*-pyrrole was coupled with 3-anisylboronic acid (Table 5, entry 6) or *N*-heterocyclic boronic acids (3-pyridylboronic acid; Table 5, entry 7).

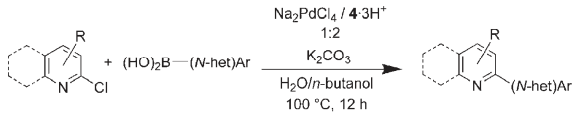
Because of its ubiquitous appearance in natural products, compounds bearing an indole ring are of importance for pharmaceutical chemistry[77] as, for example, antitumor agents.[78,79] Suzuki couplings of aryl halides with the corresponding indoleboronic acids should thus represent a convenient approach for the introduction of this heterocycle. In a comprehensive study of the reactivity of haloindoles and indoleboronic acids in Suzuki cross-couplings, Giralt et al.[30] noted that unprotected indoleboronic acid is not well suited for Suzuki reactions. It is thus not surprising that most of the known cross-coupling protocols either utilize *N*-protected indoleboronic acids,[80] accepting the need for a protection/deprotection sequence, or otherwise are restricted to the use of the more active aryl bromides as coupling partners.[29,34,41,81,82] Recently, the use of improved catalysts and modified reaction protocols has allowed the coupling of aryl chlorides with unprotected indoleboronic acids—unfortunately, though, this requires catalyst loadings of 2–5 mol%.[33,35,72]

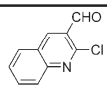
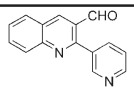
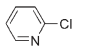
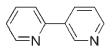
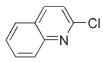
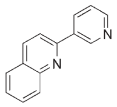
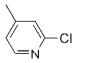
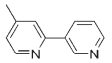
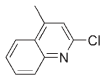
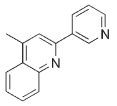
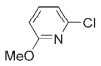
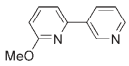
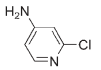
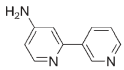
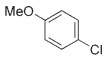
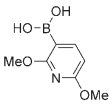
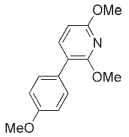
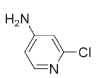
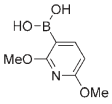
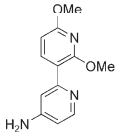
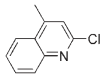
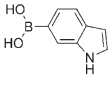
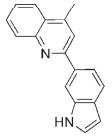
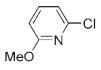
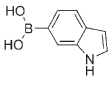
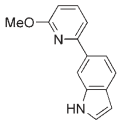
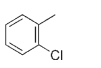
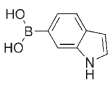
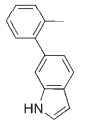
With our newly developed reaction protocol (Table 4), catalyst loadings of only 0.05 mol% [Pd/**4**] are sufficient to couple indole-6-boronic acid with *N*-heterocyclic aryl chlorides such as 2-chloro-6-methoxypyridine (Table 4, entry 11) in 95% yield. Even deactivated and sterically hindered aryl chlorides such as 2-chlorotoluene were coupled under the same conditions in 91% yield (Table 4, entry 12). In the absence of *N*-protecting groups, the Suzuki pathway is the preferred one.

Suzuki coupling of purines: Purines, the core bases of the DNA and RNA nucleotide building blocks adenine and guanine, represent an important class of biologically active compounds and are used as antiviral[83–87] or anticancer agents.[85,88–93] Suzuki couplings have been used to introduce various substituted aryl groups into purine systems.[89,94] However, unprotected halo-9*H*-purine bases proved to be unreactive in common cross-coupling protocols, due to removal of the *N*9 proton.[44,95] Cross-coupling proceeded only when *N*9 was decorated with a protective group, although high Pd catalyst loadings (at least 5 mol%) combined with elevated reaction temperatures were still required.[88,89,94,96–98] Recently, Shaughnessy and co-workers reported improved Suzuki arylations of unprotected bromonucleosides in the presence of water-soluble arylphosphine Pd complexes in aqueous media, eliminating the need for protection/deprotection steps.[25,60] An extension of this method for cross-coupling of free chloropurine bases offering high-yielding cross-couplings was reported by Hocek, but again excessive amounts of catalyst (5–10 mol%) combined with microwave irradiation were required.[59] Interestingly, the use of highly water-soluble ligands is essential for the reported protocols. Shaughnessy and Hocek independently demonstrated that highly water-soluble ligands—such as triphenylphosphine-trissulfonate (TPPTS)—have a significant higher catalytic activity in Suzuki couplings of halopurines than poorly soluble phosphine ligands.[25,60,99] Hence, excellent water solubility of the catalyst seems to be essential for coupling of halopurines in aqueous media.

In contrast to previous work, the Pd complex of our doubly sulfonated phosphine **4**·3H$^+$ allows Suzuki couplings of unprotected chloropurines in the presence of only 0.5 mol% catalyst. 6-Chloro-9*H*-purine was successfully Suzuki-coupled with *p*-tolylboronic acid and *m*-anisylboronic acid in 91 and 86% yields, respectively, in water/*n*-butanol as solvent (Table 6).

Table 4. Suzuki reactions with 2-chloropyridines, 2-chloroquinolines and deactivated aryl chlorides with *N*-heterocyclic boronic acids in water/*n*-butanol 1:3.[a]



Entry	Aryl chloride	Boronic acid	Product	Pd [mol%]	Conv.[b] [%]	Yield[c] [%]
1				0.01	≥99	91
2				0.01	≥99	93
3				0.01	≥99	93
4				0.01	≥99	89
5				0.01	≥99	92
6				0.05	≥99	93
7				0.05 0.02	≥99 63	90
8				0.05	≥99	92
9				0.05	97	90
10				0.05	≥99	92
11				0.05	≥99	95
12				0.05	≥99	91

[a]–[c] Same conditions as reported in Table 3.

Suzuki couplings of *S*-heterocyclic aryl chlorides: Thiophenes and *N*,*S*-heterocyclic thiazoles are abundant in natural products, and many compounds bearing thiophene moieties are of interest in pharmaceutical and fine chemistry, due to their biological activities.[20,100,101,102–110] Aryl derivatives of benzothiazole have attracted interest due to their biological activities as glutamate receptor antagonists.[28] There are a few reports on Suzuki couplings of chlorothiophenes in the presence of catalyst loadings of 1–2 mol%.[72,111,112]

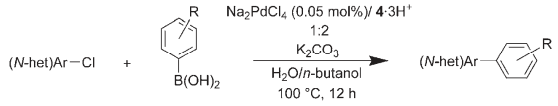
We were interested to know whether the catalyst formulation successfully applied in the synthesis of *N*-heterocycles would also be useful in the synthesis of *S*-heterocyclic biaryls. 3-Chlorothiophene was quantitatively coupled with *p*-tolylboronic acid (Table 7, entry 1) in water/*n*-butanol at 100°C in the presence of 0.05 mol% of [Pd/**4**] complex generated in situ as catalyst. Quantitative conversion was achieved in the reactions of 2-chlorothiophene with the electron-deficient 3-pyridylboronic acid (Table 7, entry 2) and of 5-chloro-2-methylbenzothiazole with *p*-tolylboronic acid (Table 7, entry 3). When 3-pyridylboronic acid was used as an electron-deficient metalloid a catalyst loading of 0.05 mol% gave 95% yield.

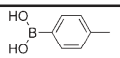
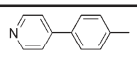
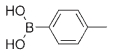
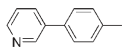
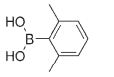
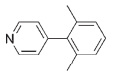
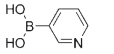
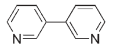
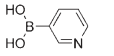
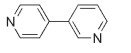
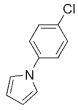
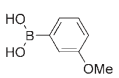
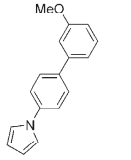
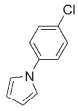
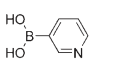
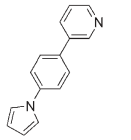
The reaction protocol used for the *N*-heterocycles can thus also be applied to the *S*-heterocycles with use of between 0.01–0.05 mol% of catalyst with quantitative conversion of the substrates.

Summary and Conclusions

A disulfonated sterically demanding and electron-rich flu-

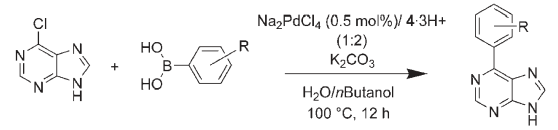
Table 5. Suzuki reactions with several activated and deactivated *N*-heterocyclic aryl chlorides in water/*n*-butanol 1:3.[a]

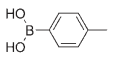
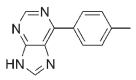
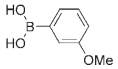
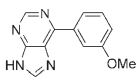


Entry	Aryl chloride	Boronic acid	Product	Conv. [%][b]	Yield [%][c]
1				≥99	95
2				≥99	93
3				≥99	93
4				≥99	94
5				≥99	95
6				≥99	94
7				≥99	90

[a]–[c] Same conditions as reported in Table 3.

Table 6. Suzuki reactions with 6-chloropurine in water/*n*-butanol 1:3.[a]



Entry	Aryl chloride	Boronic acid	Product	Conv. [%][b]	Yield [%][c]
1				97	91
2				94	86

[a], [b] Same conditions as reported in Table 3. [c] Average of two runs; products were isolated by column chromatography (silica gel), CH_2Cl_2/MeOH/NEt_3 5:1:1.

orenylphosphine (**4**) was synthesized in three steps from simple commercially available starting materials in 64% overall yield on a 50 g scale. The corresponding air-stable phosphonium salt (**4**·3H$^+$) is readily deprotonated under cross-coupling conditions and forms a highly water-soluble Pd complex with [Na_2PdCl_4]. We have demonstrated for various substrate combinations that chloropyridines (-quinolines) and aryl chlorides can be Suzuki-coupled with aryl-, pyridine- or indoleboronic acids in quantitative yields in water/*n*-butanol solvent, in the presence of between 0.005–0.05 mol% of this Pd catalyst at 100°C. Chloropurines are quantitatively Suzuki-coupled in the presence of 0.5 mol% of catalyst. *S*-Heterocyclic aryl chlorides and aryl- or 3-pyridylboronic acids require 0.01–0.05 mol% Pd catalyst for full conversion.

Essential for the superior performance of the disulfonated fluorenylphosphine in the Suzuki coupling of heterocyclic substrates is the rational reaction design, based on the excellent water solubility of the Pd catalyst, the electron-rich and sterically demanding nature of the phosphine ligand, the good solubility of all reactants in the *n*-butanol/water (3:1) solvent mixture, the presence of a significant amount of water in the reaction solvent and the monophasic nature of the reaction mixture at the reaction temperatures.

All of these properties combined furnish a catalyst of unprecedented activity for Suzuki couplings of a broad range of *N*- and *S*-heterocyclic substrates.

Experimental Section

All chemicals were purchased as reagent grade from commercial suppliers and were used without further purification, unless otherwise noted. Solvents used (water, *n*-butanol, all technical grade) were deaerated by the freeze and thaw technique (2×). Potassium carbonate used in cross-coupling reactions was technical grade. The phosphine ligands PhenPropFluPCy$_2$·HBF$_4$ (**3**) and PropPhenFluPCy$_2$DS (**4**·3H$^+$) are also commercially available under the trade name *cataCXium F* and *cataCXium F sulf* from Evonik–Degussa GmbH. All experiments were carried out under argon unless otherwise noted. Proton (^{1}H NMR), carbon (^{13}C NMR), phosphorus (^{31}P NMR) and nitrogen (^{15}N NMR) nuclear magnetic resonance spectra were recorded on a Bruker DRX 500 instrument at 500 MHz, 125.75 MHz, 202.46 MHz and 50.69 MHz, respectively at 293 K. The chemical shifts are given in parts per million (ppm) on the delta scale (δ) and are referenced to tetramethylsilane ($\delta = 0$ ppm,

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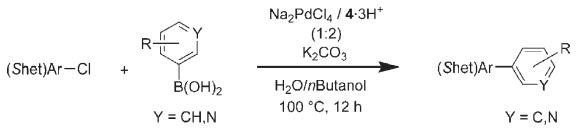
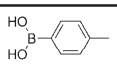
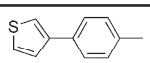
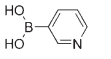
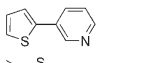
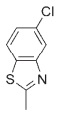
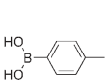
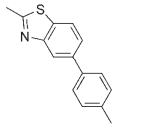
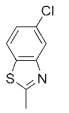
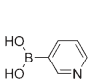
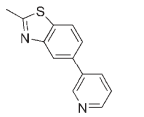
Table 7. Suzuki reactions of *S*-heterocyclic chlorides in *n*-butanol/water 1:3.[a]



Entry	Aryl chloride	Boronic acid	Product	Pd [mol%]	Conv. [%][b]	Yield%[c]
1				0.05	≥99	93
2				0.05	≥99	90
3				0.01	≥99	89
4				0.05	≥99	95

[a]–[c] Same conditions as reported in Table 3.

^{1}H NMR), 65% aq. H_3PO_4 ($\delta = 0$ ppm, ^{31}P NMR) and nitromethane ($\delta = 0$ ppm, ^{15}N NMR). Abbreviations for NMR data: s = singlet, d = doublet, t = triplet, q = quartet, qi = quintet, dd = doublet of doublets, dt = doublet of triplets, dq = doublet of quartets, tt = triplet of triplets, m = multiplet, br = broad. Selected NMR spectra are given in the Supporting Information. Mass spectra were recorded on a Finnegan MAT 95 magnetic sector spectrometer. Thin layer chromatography (TLC) was performed on Fluka silica gel 60 F 254 (0.2 mm) on aluminum plates. Silica gel columns for chromatography were prepared with E. Merck silica gel 60 (0.063–0.20 mesh ASTM). Quantitative elemental analyses were performed on a Vavio Micro instrument (Elementar Analysensysteme, GmbH, Germany). GC experiments were run on a Clarus 500 GC with autosampler and FID detector. Column: Varian CP-Sil 8 CB (l = 15 m, di = 0.25 mm, dF = 1.0 μm), N_2 (flow: 17 cm sec^{-1}; split 1:50). Injector temperature: 270°C, detector temperature: 350°C. Temperature program: isotherm 150°C for 5 min, heating to 300°C at 25°C min^{-1}, isotherm for 15 min. 9-(3-Phenylpropyl)-9*H*-fluorene (**2**) was prepared by a published procedure.[70]

9-(3-Phenylpropyl)FluPCy$_2$·HBF$_4$ (3·H$^+$): 9-(3-Phenylpropyl)-9*H*-fluorene (**2**, 117 g, 0.410 mol) was suspended in dry methyl *tert*-butyl ether (MTBE, 2.7 L) under argon in a 6 L three-necked round-bottomed flask. *n*BuLi (2.5 M in hexane, 162 mL, 0.406 mol) was added at 0°C over 10 min. The reaction mixture was warmed to 20°C, forming a deep red, clear solution that was stirred for an additional 2 h at ambient temperature. The mixture was then cooled to −30°C, and Cy_2PCl (92.75 g, 0.399 mol) was added over 10 min. The red color disappeared to form a yellow clear solution, which was stirred for an additional 1 h at 20°C (precipitation of LiCl started after about 20 min). The suspension was extracted with degassed water (1×750 mL) to remove the LiCl. The clear, slightly yellowish organic layer was treated with aqueous HBF_4 (48%, 59 mL, 0.451 mol) with vigorous stirring over 2 min to precipitate the title compound as white crystals. More HBF_4 (25 mL, 2 M in water) was added, the suspension was stirred for another 10 min, and the precipitate was then separated by suction filtration (glass frit G3) and washed with MTBE (2×100 mL). Drying of the product at 60°C in vacuo afforded **3**·H$^+$ (208 g, 92%) as white crystals. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.85$ (d, $^3J = 7.5$ Hz, 2H; *CH*, ar), 7.69 (d, $^3J = 7.5$ Hz, 2H; *CH*, ar), 7.56 (t, $^3J = 7.0$ Hz, 2H; C*H*, ar), 7.48 (t, $^3J = 7.5$ Hz, 2H; *CH*, ar), 7.20–7.14 (m, 2H; C*H*, ar), 7.14–7.01 (m, 1H; C*H*, ar), 6.92 (d, $^3J = 7.5$ Hz, 2H; C*H*, ar), 6.47 (d, $^1J = 479.5$ Hz, 1H; P*H*), 2.75–2.67 (m, 2H; Flu-CH_2), 2.47 (t, $^3J = 7.5$ Hz, 2H; Ph-CH_2), 2.23–2.11 (m, 2H; *CH*), 1.87–1.01 (m, 20H; Cy-CH_2), 0.93–0.84 ppm (m, 2H; CH_2-CH_2-CH_2); ^{13}C{^{1}H} NMR (125.8 MHz, $CDCl_3$): $\delta = 141.4$ (d, $J_{PC} = 4.3$ Hz), 141.1, 139.9 (d, $J_{PC} = 1.8$ Hz), 130.3, 129.2, 128.4, 128.3, 126.0, 125.0, (d, $J_{PC} = 1.8$ Hz), 121.1, 52.3 (d, $J_{PC} = 34.2$ Hz), 34.9, 32.9, 31.2 (d, $J_{PC} = 34.1$ Hz), 29.4 (d, $J_{PC} = 3.6$ Hz), 28.0 (d, $J_{PC} = 3.5$ Hz), 26.8, 26.7, 26.6, 26.5, 24.9, 24.3, 24.2 ppm; ^{31}P{^{1}H} NMR (202.5 MHz, $CDCl_3$): $\delta = 35.6$ ppm; ^{31}P NMR (202.5 MHz, $CDCl_3$): $\delta = 35.6$ ppm (d, $J_{PH} = 477.5$ Hz); elemental analysis calcd (%) for $C_{34}H_{42}BF_4P$: C 71.83, H 7.45; found: C 71.54, H 7.40.

PropPhenFluPCy$_2$DS disodium salt (4): 9-(3-Phenylpropyl)FluCy$_2$·HBF_4 (**3**·H$^+$, 400 mg, 0.70 mmol) was dissolved in CH_2Cl_2 (2 mL) in a 25 mL Schlenk tube. After addition of conc. H_2SO_4 (1 mL, 18.8 mmol) the solution was stirred overnight at 50°C. The solution was added dropwise to ice; in the end a clear colorless solution was obtained. After degassing of this solution, it was neutralised with NaOH (20% solution in degassed water), in the presence of degassed phenolphthaleine solution as an indicator. The water was removed in vacuo until Na_2SO_4 started to precipitate. Degassed MeOH (10 mL) was then added to precipitate most of the Na_2SO_4, which was removed by filtration to give a clear filtrate. Removal of the volatiles in vacuo afforded **4** (412 mg, 86%) as a white solid. ^{1}H NMR (500 MHz, CD_3OD): $\delta = 7.97$ (s, 1H; C*H*, ar), 7.89–7.85 (m, 3H; C*H*, ar), 7.66–7.61 (m, 2H; C*H*, ar), 7.43–7.30 (m, 3H; C*H*, ar), 7.97 (d, $^3J = 8.0$ Hz, 2H; C*H*, ar), 2.53–2.29 (m, 4H; CH_2), 2.00–0.73 ppm (m, 24H; C*H*+CH_2); ^{13}C{^{1}H} NMR (125.77 MHz, CD_3OD): $\delta = 151.2$, 150.2, 146.3, 145.3, 144.4, 144.0, 141.5, 129.6, 129.3, 128.6, 127.3, 126.4, 125.5 (d, $J_{PC} = 5.1$ Hz), 123.2 (d, $J_{PC} = 3.3$ Hz), 121.8, 121.0, 57.1 (d, $J_{PC} = 28.5$ Hz), 38.8 (d, $J_{PC} = 22.7$ Hz), 36.8, 35.2, 35.0, 34.9, 34.7, 34.7, 34.6, 34.5, 31.6 (d, $J_{PC} = 10.4$ Hz), 31.1 (d, $J_{PC} = 7.5$ Hz), 29.2 (d, $J_{PC} = 13.1$ Hz), 28.9, 28.8, 28.8, 28.5 (d, $J_{PC} = 7.03$ Hz), 27.8, 27.6, 27.4, 27.2, 26.9 (d, $J_{PC} = 10.4$ Hz), 26.2 ppm; ^{31}P{^{1}H} NMR (202.46 MHz, CD_3OD): $\delta = 33.6$ ppm; MS (70 eV): *m/z*: 700 $[M+O]^+$, 684 $[M]^+$, 601 $[M-Cy]^+$.

PropPhenFluPCy$_2$DS·H$_2$SO$_4$ (4b·3H$^+$): Concentrated sulfuric acid (270 mL, 5 mol) was added at 0°C under argon to a solution of 9-(3-phenylpropyl)FluPCy$_2$·HBF_4 (**3**·H$^+$, 50 g, 0.88 mol) in CH_2Cl_2 (100 mL, technical grade). The reaction mixture was warmed up to 50°C with stirring. After removal of the $CHCl_2$, the reaction mixture was stirred at 50°C overnight. The clear, slightly yellow solution was poured onto ice (1500 g). The white precipitate was separated by suction filtration and washed with ice water (2×100 mL). The precipitate was dissolved in MeOH (300 mL) and filtered, and the clear, colorless filtrate was added dropwise to MTBE (1600 mL, vigorously stirred) to precipitate the product. Decantation of the solvent and removal of the volatiles in vacuo afforded the pure product (**4**·3H$^+$) (50.3 g, 77%) as a white solid. ^{1}H NMR (500 MHz, CD_3OD): $\delta = 8.26$ (s, 1H; C*H*, ar), 8.13–8.08 (m, 3H; C*H*, ar), 7.73 (d, $^3J = 8.0$ Hz, 1H; C*H*, ar), 7.69–7.64 (m, 1H; C*H*, ar), 7.67 (d, $^3J = 8.5$ Hz, 2H; C*H*, ar), 7.57 (dt, $^5J = 0.5$, 7.0 Hz, 1H; C*H*, ar), 7.04 (d, $^3J = 8.5$ Hz, 2H; C*H*, ar), 2.89–2.80 (m, 1H; C*H*), 2.74–2.62 (m, 2H; C*H* and CH_2), 2.59–2.45 (m, 2H; CH_2), 2.44–2.33 (m, 1H; CH_2), 1.92–1.83 (m, 1H; CH_2), 1.80–0.93 (m, 20H; CH_2), 0.87–0.76 ppm (m, 1H; CH_2); ^{13}C NMR (125.77 MHz, CD_3OD): $\delta = 147.6$, 145.6, 145.1 (d, $J_{PC} = 4.4$ Hz), 144.2, 142.5 (d, $J_{PC} = 4.8$ Hz), 142.4 (d, $J_{PC} = 2.8$ Hz), 141.7 (d, $J_{PC} = 4.2$ Hz), 132.2, 131.2, 129.8, 129.7, 127.6, 126.8 (d, $J_{PC} = 3.9$ Hz), 124.4 (d, $J_{PC} = 3.9$ Hz), 123.6, 122.9, 53.7 (d, $J_{PC} = 33.5$ Hz), 35.8, 34.5, 32.7 (d, $J_{PC} = 3.8$ Hz), 32.5 (d, $J_{PC} = 4.0$ Hz), 31.2 (d, $J_{PC} = 3.9$ Hz), 30.6 (d, $J_{PC} = 3.5$ Hz), 30.0 (d, $J_{PC} = 3.3$ Hz), 29.8 (d, $J_{PC} = 3.3$ Hz), 28.1, 28.0, 28.0, 27.9, 27.9, 27.8, 27.8, 27.7, 26.4 (d, $J_{PC} = 1.5$ Hz), 25.4, 25.3 ppm; ^{31}P {^{1}H} NMR

(202.46 MHz, CD_3OD): $\delta = 34.2$ ppm; MS (70 eV): *m/z*: 641 $[M-HSO_4]^+$, 639 $[M-H_2SO_4-H]$, 442 $[M-H_2SO_4-PCy_2-H]$.

General procedure for Suzuki cross-coupling reactions in aqueous *n*-butanol

Preparation of catalyst stock solution: $[Na_2PdCl_4]$ (5.9 mg, 0.02 mmol), PropPhenFluPCy$_2$DS·H_2SO_4 (**4**·3H^+, 30 mg, 0.04 mmol) and K_2CO_3 (33 mg, 0.24 mmol) were placed in a 25 mL Schlenk tube and evacuated and backfilled with Ar thrice. Degassed water (20 mL) was added, and the mixture was stirred at 55 °C for 3 h to provide a clear, nearly colorless solution. The $c_{[Pd]}$ of this catalyst stock solution is 0.001 mmol mL^{-1}.

Cross-coupling reaction: The boronic acid (1.2 mmol) and K_2CO_3 (440 mg, 3.2 mmol) were placed in a 25 mL Schlenk tube and evacuated and backfilled with Ar thrice. Degassed water (1 mL) and degassed *n*-butanol (3 mL) were then added together with the aryl halide (1 mmol) and the appropriate volume of catalyst stock solution (e.g., 1 mL of the solution prepared above was added to obtain a catalyst loading of 0.1 mol%). The reaction mixture was stirred for 12 h at 100 °C and then cooled to room temperature. Water (5 mL) was added and the product was extracted with methyl *tert*-butyl ether (2×5 mL). The organic layer was concentrated in vacuo, and the residue was purified by column chromatography (silica (20×3 cm), cyclohexene/EtOAc/NEt_3 (10:1:1) as eluent) to afford the pure corresponding cross-coupling product in 86–96% yield.

Analytical data for the Suzuki products

2-*p*-Tolylpyridine (Table 3, entry 1): The NMR spectra were identical to those in the literature.[113]

2-*p*-Tolylisonicotinonitrile (Table 3, entry 2): ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 8.75$ (dd, $^5J = 0.5$, $^5J = 5.0$ Hz, 1H; C*H*, ar), 7.84–7.80 (m, 3H; C*H*, ar), 7.32 (dd, $^4J = 1.0$, $^3J = 5.0$ Hz, 1H; C*H*, ar), 7.24 (d, $^3J = 8.0$ Hz, 2H; C*H*, ar), 2.35 ppm (s, 3H; CH_3); $^{13}C\{^1H\}$ NMR (125.77 MHz, $CDCl_3$): $\delta = 157.7$, 149.5, 139.5, 133.5, 128.8, 125.8, 121.8, 120.7, 120.1, 115.8, 20.3 ppm; HRMS: *m/z*: calcd for $C_{13}H_{10}N_2$: 194.0844; found: 194.08414.

2-*p*-Tolylquinoline-3-carbaldehyde (Table 3, entry 3): ^{1}H NMR (500 MHz, CD_3CN): $\delta = 10.12$ (s, 1H; C*H*O), 8.85 (s, 1H; C*H*, ar), 8.14–8.09 (m, 3H; C*H*, ar), 7.91 (ddd, $^5J = 1.5$, $^3J = 7.0$, 8.5 Hz, 1H; C*H*, ar), 7.76 (ddd, $^5J = 1.5$, $^3J = 7.0$, 8.5 Hz, 1H; C*H*, ar), 7.59 (td, $^4J = 2.0$, $^3J = 8.0$ Hz, 2H; C*H*, ar), 7.41–7.38 (m, 2H; C*H*, ar), 2.45 ppm (s, 3H; CH_3); $^{13}C\{^1H\}$ NMR (125.77 MHz, CD_3CN): $\delta = 191.1$, 159.6, 149.1, 139.2, 137.9, 135.1, 132.3, 130.0, 129.3, 128.8, 128.8, 127.7, 127.1, 126.0, 20.1 ppm; HRMS: *m/z*: calcd for $C_{17}H_{13}NO$: 247.0997; found: 247.09700.

4-Methyl-2-*p*-tolylquinoline (Table 3, entry 4): The NMR spectra were identical to those in the literature.[114]

4-Methyl-2-*p*-tolylpyridine (Table 3, entry 5): The NMR spectra were identical to those in the literature.[115]

2-*p*-Tolylquinoline (Table 3, entry 6): The NMR spectra were identical to those in the literature.[115]

2-Methoxy-6-*p*-tolylpyridine (Table 3, entry 7): ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.93$ (d, $^3J = 8.5$ Hz, 2H; C*H*, ar), 7.58 (dd, $^3J = 7.5$, 8.0 Hz, 1H; C*H*, ar), 7.29 (dd, $^5J = 0.5$, $^3J = 7.5$ Hz, 1H; C*H*, ar), 7.24 (dd, $^5J = 0.5$, $^3J = 8.5$ Hz, 2H; C*H*, ar), 6.64 (d, $^3J = 8.0$ Hz, 1H; C*H*, ar), 4.02 (s, 3H; OCH_3), 2.39 ppm (s, 3H; CH_3); $^{13}C\{^1H\}$ NMR (125.77 MHz, $CDCl_3$): $\delta = 164.1$, 155.2, 139.5, 139.2, 136.8, 129.7, 127.0, 112.8, 109.2, 53.5, 21.7 ppm; HRMS: *m/z*: calcd for $C_{13}H_{13}NO$: 199.0997; found: 199.09999.

2-*p*-Tolylpyridin-4-ylamine (Table 3, entry 8): ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 8.25$ (d, $^3J = 5.5$ Hz, 1H; ar), 7.78 (d, $^3J = 8.0$ Hz, 2H; ar), 7.21 (d, $^3J = 8.0$ Hz, 2H; ar), 6.85 (s, 1H; ar), 6.39 (dd, $^3J = 5.5$, $^4J = 2.5$ Hz, 1H; ar), 4.35 (brs, 2H; NH_2), 2.36 ppm (s, 3H; CH_3); $^{13}C\{^1H\}$ NMR (125.77 MHz, $CDCl_3$): $\delta = 157.2$, 152.6, 159.0, 137.6, 136.0, 128.2, 125.7, 107.2, 105.1, 20.2 ppm; HRMS: *m/z*: calcd for $C_{12}H_{12}N_2$: 184.1001; found: 184.09808.

4-Methyl-2-*m*-tolylquinoline (Table 3, entry 9): ^{1}H NMR (500 MHz, CD_3CN): $\delta = 8.06$–8.01 (m, 3H; C*H*, ar), 7.99–7.96 (m, 1H; C*H*, ar), 7.82 (d, $^5J = 0.5$ Hz, 1H; C*H*, ar), 7.71 (ddd, $^5J = 1.5$, $^3J = 6.5$, 8.5 Hz, 1H; C*H*, ar), 7.55 (ddd, $^5J = 1.0$, $^3J = 6.5$, 8.5 Hz, 1H; C*H*, ar), 7.40 (t, $^3J = 8.0$ Hz, 1H; C*H*, ar), 7.30–7.27 (m, 1H; C*H*, ar), 2.71 (d, $^5J = 0.5$ Hz, 3H; CH_3), 2.44 ppm (s, 3H; CH_3); $^{13}C\{^1H\}$ NMR (125.77 MHz, CD_3CN): $\delta = 156.2$, 147.6, 144.9, 139.1, 138.1, 129.7, 129.5, 129.0, 128.3, 127.6, 126.9, 125.7, 124.1, 123.6, 119.0, 20.3, 17.7 ppm; HRMS: *m/z*: calcd for $C_{17}H_{15}N$: 233.1205; found: 233.12109.

4-Methyl-2-(3-trifluoromethyl-phenyl)-quinoline (Table 3, entry 10): ^{1}H NMR (500 MHz, CD_3CN): $\delta = 8.54$ (s, 1H; C*H*, ar), 8.41 (d, $^3J = 7.0$ Hz, 1H; C*H*, ar), 8.08–8.02 (m, 2H; C*H*, ar), 7.87–7.85 (m, 1H; C*H*, ar), 7.78–7.71 (m, 2H; C*H*, ar), 7.68 (t, $^3J = 7.5$ Hz, 1H; C*H*, ar), 7.60–7.56 (m, 1H; C*H*, ar), 2.73–2.72 ppm (m, 3H; CH_3); $^{13}C\{^1H\}$ NMR (125.77 MHz, CD_3CN): $\delta = 154.2$, 147.5, 145.6, 140.0, 130.5, 130.1 (q, $^2J = 31.8$ Hz, CCF_3), 129.6, 129.3, 129.3, 127.1, 126.2, 125.4 (q, $^3J = 4.4$ Hz, $CHCCF_3$), 123.7, 124.2 (q, $^1J = 271.8$ Hz, CF_3), 123.5 (q, $^3J = 2.9$ Hz, $CHCCF_3$), 118.7, 17.7 ppm; HRMS: *m/z*: calcd for $C_{17}H_{12}NF_3$: 287.0922; found: 287.09206.

2-*m*-Tolylquinoline-3-carbaldehyde (Table 3, entry 11): ^{1}H NMR (500 MHz, CD_3CN): $\delta = 10.10$ (s, 1H; C*H*O), 8.83 (s, 1H; C*H*, ar), 8.12–8.08 (m, 2H; C*H*, ar), 7.90 (ddd, $^5J = 1.5$, $^3J = 7.0$, 9.0 Hz, 1H; C*H*, ar), 7.67 (ddd, $^5J = 1.0$, $^3J = 7.0$, 8.0 Hz, 1H; C*H*, ar), 7.53–7.50 (m, 1H; C*H*, ar), 7.46–7.43 (m, 2H; C*H*, ar), 7.40–7.35 (m, 1H; C*H*, ar), 2.45 ppm (s, 3H; CH_3); $^{13}C\{^1H\}$ NMR (125.77 MHz, CD_3CN): $\delta = 191.0$, 159.8, 149.0, 138.1, 137.9, 137.8, 132.3, 130.4, 129.5, 129.3, 128.8, 128.0, 127.6, 127.2, 127.1, 126.0, 20.2 ppm; HRMS: *m/z*: calcd for $C_{17}H_{13}NO$: 247.0997; found: 247.09813.

2-(3-Trifluoromethyl-phenyl)-quinoline-3-carbaldehyde (Table 3, entry 12): ^{1}H NMR (500 MHz, CD_3CN): $\delta = 10.10$ (s, 1H; C*H*O), 8.87 (s, 1H; C*H*, ar), 8.15–8.10 (m, 2H; C*H*, ar), 8.03 (s, 1H; C*H*, ar), 7.93 (ddd, $^5J = 1.5$, $^3J = 7.0$, 8.5 Hz, 1H; C*H*, ar), 7.91–7.84 (m, 2H; C*H*, ar), 7.76–7.68 ppm (m, 2H; C*H*, ar); $^{13}C\{^1H\}$ NMR (125.77 MHz, CD_3CN): $\delta = 190.6$, 157.7, 148.9, 139.3, 139.2, 133.6, 132.6, 129. (q, $^2J = 32.3$ Hz, CCF_3), 129.2, 128.9, 128.9, 127.6, 127.5, 126.3 (q, $^3J = 3.9$ Hz, $CHCCF_3$), 126.2, 125.3 (q, $^3J = 3.8$ Hz, $CHCCF_3$), 124.0 ppm (q, $^1J = 272.4$ Hz, CF_3); HRMS: *m/z*: calcd for $C_{17}H_{10}NOF_3$: 301.0714; found: 301.06928.

2-Naphthalen-1-yl-quinoline-3-carbaldehyde (Table 3, entry 13): ^{1}H NMR (500 MHz, CD_3CN): $\delta = 9.74$ (s, 1H; C*H*O), 8.96 (s, 1H; C*H*, ar), 8.22 (d, $^3J = 8.0$ Hz, 1H; C*H*, ar), 8.13 (dd, $^5J = 0.5$, $^3J = 8.5$ Hz, 1H; C*H*, ar), 8.09 (d, $^3J = 8.0$ Hz, 1H; C*H*, ar), 8.04 (d, $^3J = 8.0$ Hz, 1H; C*H*, ar), 7.96 (ddd, $^5J = 1.0$, $^3J = 6.5$, 8.5 Hz, 1H; C*H*, ar), 7.75 (ddd, $^5J = 1.5$, $^3J = 7.0$, 8.5 Hz, 1H; C*H*, ar), 7.67 (dd, $^3J = 7.0$, 8.0 Hz, 1H; C*H*, ar), 7.62–7.52 (m, 3H; C*H*, ar), 7.44 ppm (ddd, $^5J = 1.5$, $^3J = 7.0$, 8.5 Hz, 1H; C*H*, ar); $^{13}C\{^1H\}$ NMR (125.77 MHz, CD_3CN): $\delta = 190.6$, 159.2, 149.3, 137.8, 135.6, 133.2, 132.5, 131.8, 129.5, 128.9, 128.8, 128.8, 128.1, 127.9, 127.5, 126.6, 126.4, 126.0, 125.0, 125.0 ppm; HRMS: *m/z*: calcd for $C_{20}H_{13}NO$: 283.0997; found: 283.09811.

2-Naphthalen-1-ylpyridine (Table 3, entry 14): The NMR spectra were identical to those in the literature.[116]

2-Naphthalen-1-ylquinoline (Table 3, entry 15): The NMR spectra were identical to those in the literature.[117]

2-Naphthalen-1-ylpyridin-4-ylamine (Table 3, entry 16): ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 8.20$ (d, $^3J = 5.5$ Hz, 1H; ar), 8.01 (d, $^3J = 8.0$ Hz, 1H; ar), 7.76 (t, $^3J = 9.5$ Hz, 2H; ar), 7.43–7.33 (m, 4H; ar), 6.47 (d, $^4J = 2.0$ Hz, 1H; ar), 6.27 (dd, $^3J = 5.5$, $^4J = 2.5$ Hz, 1H; ar), 4.37 ppm (brs, 2H; NH_2); $^{13}C\{^1H\}$ NMR (125.77 MHz, $CDCl_3$): $\delta = 158.5$, 152.4, 148.5, 138.0, 132.7, 130.2, 127.4, 127.1, 125.8, 125.1, 124.9, 124.7, 124.1, 109.6, 107.1 ppm; HRMS: *m/z*: calcd for $C_{15}H_{12}N_2$: 220.1001; found: 220.09869.

4-Methyl-2-naphthalen-1-ylquinoline (Table 3, entry 17): The NMR spectra were identical to those in the literature.[118]

1-Naphthylisonicotinonitrile (Table 3, entry 18): ^{1}H NMR (500 MHz, CD_3CN): $\delta = 8.75$ (dd, $^5J = 0.5$ Hz, $^3J = 5.0$ Hz, 1H; C*H*, ar), 8.75 (dd, $^4J = 2.5$ Hz, $^3J = 6.5$ Hz, 1H; C*H*, ar), 7.82–7.81 (m, 1H; C*H*, ar), 7.81–7.79 (m, 2H; C*H*, ar), 7.58 (dd, $^5J = 1.5$ Hz, $^3J = 5.5$ Hz, 1H; C*H*, ar), 7.45–7.42 (m, 2H; C*H*, ar), 7.38 (ddd, $^5J = 1.0$ Hz, $^3J = 7.0$ Hz, $^3J = 7.5$ Hz, 1H; C*H*, ar), 7.34 ppm (ddd, $^5J = 1.0$ Hz, $^3J = 6.5$ Hz, $^3J = 8.0$ Hz, 1H; C*H*, ar); $^{13}C\{^1H\}$ NMR (125.77 MHz, CD_3CN): $\delta = 159.2$, 149.6, 135.6, 133.5, 130.3, 129.6, 128.2, 127.8, 127.0, 126.7, 126.1, 125.1, 124.7, 124.0, 121.2, 116.3 ppm; HRMS: *m/z*: calcd for $C_{16}H_{10}N_2$: 230.0844; found: 230.08168.

2-Methoxy-6-naphthalen-1-ylpyridine (Table 3, entry 19): The NMR spectra were identical to those in the literature.[119]

2-Pyridin-3-ylquinoline-3-carbaldehyde (Table 4, entry 1): ^{1}H NMR (500 MHz, CD_3CN): δ = 10.15 (s, 1H; C*H*O), 8.93 (s, 1H; C*H*, ar), 8.87 (d, ^5J = 1.5 Hz, 1H; C*H*, ar), 8.73 (dd, ^5J = 1.5 Hz, ^3J = 4.5 Hz, 1H; C*H*, ar), 8.19–8.14 (m, 2H; C*H*, ar), 8.07–8.04 (m, 1H; C*H*, ar), 7.96 (ddd, ^5J = 1.0 Hz, ^3J = 6.5 Hz, ^3J = 8.5 Hz, 1H; C*H*, ar), 7.73 (ddd, ^5J = 1.0 Hz, ^3J = 7.0 Hz, ^3J = 8.0 Hz, 1H; C*H*, ar), 7.54 ppm (ddd, ^5J = 0.5 Hz, ^3J = 4.5 Hz, ^3J = 8.0 Hz, 1H; C*H*, ar); ^{13}C{^{1}H} NMR (125.77 MHz, CD_3CN): δ = 190.7, 156.5, 150.1, 149.6, 149.0, 139.6, 137.1, 132.7, 129.3, 128.9, 127.7, 127.7, 126.2, 123.9, 122.9 ppm; HRMS: *m/z*: calcd for $C_{15}H_{10}N_2O$: 234.0793; found: 234.07699.

[2,3′]Bipyridinyl (Table 4, entry 2): The NMR spectra were identical to those in the literature.[120]

2-Pyridin-3-ylquinoline (Table 4, entry 3): The NMR spectra were identical to those in the literature.[121,122]

4-Methyl-[2,3′]bipyridinyl (Table 4, entry 4): The NMR spectra were identical to those in the literature.[20]

4-Methyl-2-pyridin-3-ylquinoline (Table 4, entry 5): The NMR spectra were identical to those in the literature.[123]

6-Methoxy-[2,3′]bipyridinyl (Table 4, entry 6): The NMR spectra were identical to those in the literature.[124]

[2,3′]Bipyridinyl-4-ylamine (Table 4, entry 7): ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.01 (d, ^4J = 1.5 Hz, 1H; ar), 8.53 (dd, ^3J = 5.0 Hz, ^4J = 1.5 Hz, 1H; ar), 8.22 (d, ^3J = 6.0 Hz, 1H; ar), 8.16 (dt, ^3J = 8.0 Hz, ^4J = 2.0 Hz, 1H; ar), 6.29–6.26 (m, 1H; ar), 6.87 (d, ^4J = 2.0 Hz, 1H; ar), 6.44 (dd, ^3J = 6.0 Hz, ^4J = 2.5 Hz, 1H; ar), 4.53 ppm (s, 2H; NH_2); ^{13}C{^{1}H} NMR (125.77 MHz, $CDCl_3$): δ = 154.5, 152.8, 149.5, 148.6, 147.1, 134.4, 133.4, 122.5, 107.9, 105.5 ppm; HRMS: *m/z*: calcd for $C_{10}H_9N_3$: 171.0797; found: 171.07820.

2,6-Dimethoxy-3-(4-methoxyphenyl)pyridine (Table 4, entry 8): ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.52 (d, ^3J = 8.0 Hz, 1H; C*H*, ar), 7.45 (d, ^3J = 9.0 Hz, 2H; C*H*, ar), 6.93 (d, ^3J = 9.0 Hz, 2H; C*H*, ar), 6.36 (d, ^3J = 8.0 Hz, 1H; C*H*, ar), 3.96 (s, 3H; O$CH_{3\,Pyr}$), 3.95 (s, 3H; O$CH_{3\,Pyr}$), 3.82 ppm (s, 3H; O$CH_{3\,(Anis)}$); ^{13}C{^{1}H} NMR (125.77 MHz, $CDCl_3$): δ = 162.3, 159.6, 159.0, 141.6, 130.4, 129.7, 115.9, 114.1, 101.3, 55.7, 54.0, 53.8 ppm; HRMS: *m/z*: calcd for $C_{14}H_{15}NO_3$: 245.1052; found: 245.10379.

2′,6′-Dimethoxy-[2,3′]bipyridinyl-4-ylamine (Table 4, entry 9): ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.27 (dd, ^3J = 5.7, J = 0.6 Hz, 1H; C*H*, ar), 8.20 (d, ^3J = 8.2 Hz, 1H; C*H*, ar), 7.21 (dd, J = 2.5, 0.6 Hz, 1H; C*H*, ar), 6.43–6.40 (m, 2H; C*H*, ar), 4.18 (brs, 2H; NH_2), 4.02 (s, 3H; OCH_3), 3.96 ppm (s, 3H; OCH_3); ^{13}C{^{1}H} NMR (125.77 MHz, $CDCl_3$): δ = 161.8, 158.7, 153.8, 151.3, 148.7, 141.3, 113.5, 108.9, 106.8, 100.5, 52.6, 52.4 ppm; HRMS: *m/z*: calcd for $C_{12}H_{13}N_3O_2$: 231.1008; found: 231.10084.

2-(1*H*-Indol-6-yl)-4-methylquinoline (Table 4, entry 10): ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.54 (brs, 1H; N*H*), 8.49–8.48 (m, 1H; C*H*, ar), 8.21 (dq, ^3J = 8.5, J = 0.6 Hz, 1H; C*H*, ar), 7.99 (dd, ^3J = 8.5, J = 1.3 Hz, 1H; C*H*, ar), 7.84 (dd, ^3J = 8.2, J = 1.6 Hz, 1H; C*H*, ar), 7.80–7.79 (m, 1H; C*H*, ar), 7.73 (d, ^3J = 8.2 Hz, 1H; C*H*, ar), 7.68 (ddd, ^3J = 8.2 Hz, ^3J = 7.0, J = 1.5 Hz, 1H; C*H*, ar), 7.51 (ddd, ^3J = 8.2 Hz, ^3J = 7.0, J = 1.3 Hz, 1H; C*H*, ar), 7.16 (t, J = 2.8 Hz, 1H; C*H*, ar), 6.54–6.52 (m, 1H; C*H*, ar), 2.76 ppm (s, 3H; CH_3); ^{13}C{^{1}H} NMR (125.77 MHz, $CDCl_3$): δ = 158.3, 148.2, 144.7, 136.5, 133.4, 129.6, 129.4, 129.1, 127.2, 126.2, 125.6, 123.7, 120.7, 120.3, 119.3, 110.9, 102.2, 19.0 ppm; ^{15}N{^{1}H} NMR (50.69 MHz, $CDCl_3$) δ = −250.3, −90.3 ppm; HRMS: *m/z*: calcd for $C_{18}H_{14}N_2$: 258.1157; found: 258.11354.

6-(6-Methoxypyridin-2-yl)-1*H*-indole (Table 4, entry 11): ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.25 (brs, 1H; N*H*), 8.12–8.11 (m, 1H; C*H*, ar), 7.80 (dd, ^3J = 8.5, J = 1.6 Hz, 1H; C*H*, ar), 7.68 (dt, ^3J = 8.5, J = 0.7 Hz, 1H; C*H*, ar), 7.59 (dd, ^3J = 8.2, 7.6 Hz, 1H; C*H*, ar), 7.35 (dd, ^3J = 7.6, J = 0.6 Hz, 1H; C*H*, ar), 7.20 (dd, J = 3.1, J = 2.2 Hz, 1H; C*H*, ar), 6.64 (dd, ^3J = 8.2, J = 0.6 Hz, 1H; C*H*, ar), 6.56–6.54 (m, 1H; C*H*, ar), 4.06 ppm (s, 3H; O$CH_{3\,Pyr}$); ^{13}C{^{1}H} NMR (125.77 MHz, $CDCl_3$): δ = 163.7, 155.8, 139.2, 136.3, 133.3, 128.6, 125.6, 120.6, 118.9, 112.7, 109.6, 108.2, 102.6, 53.2 ppm; HRMS: *m/z*: calcd for $C_{14}H_{12}N_2O$: 224.095; found: 224.09509.

6-*o*-Tolyl-1*H*-indole (Table 4, entry 12): ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.01 (brs, 1H; N*H*), 7.63 (d, ^3J = 8.2 Hz, 1H; C*H*, ar), 7.29–7.19 (m, 5H; C*H*, ar), 7.10–7.06 (m, 2H; C*H*, ar), 6.55–6.52 (m, 1H; C*H*, ar), 2.28 ppm (s, 3H; CH_3); ^{13}C{^{1}H} NMR (125.77 MHz, $CDCl_3$): δ = 141.9, 134.9, 134.7, 134.6, 129.2 (2×), 125.8, 125.5, 124.6, 123.5, 120.7, 119.0, 110.5, 101.3, 19.6 ppm; HRMS: *m/z*: calcd for $C_{15}H_{13}N$: 207.1048; found: 207.10515.

4-*p*-Tolylpyridine (Table 5, entry 1): ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.62 (dd, ^3J = 4.8, J = 1.7 Hz, 2H; C*H*, ar), 7.53 (d, ^3J = 8.0 Hz, 2H; C*H*, ar), 7.45 (dd, ^3J = 4.5, J = 1.7 Hz, 2H; C*H*, ar), 7.28 (d, ^3J = 8.0 Hz, 2H; C*H*, ar), 2.40 ppm (s, 3H; CH_3); ^{13}C{^{1}H} NMR (125.8 MHz, $CDCl_3$): δ = 150.6, 148.6, 139.6, 135.6, 130.2, 127.2, 121.8, 21.6 ppm; ^{15}N NMR (50.7 MHz, $CDCl_3$): δ = −74.2 ppm; HRMS: *m/z*: calcd for $C_{12}H_{11}N$: 169.0892; found: 169.08774.

3-*p*-Tolylpyridine (Table 5, entry 2): ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.83 (dd, ^5J = 2.4, J = 0.6 Hz, 1H; C*H*, ar), 8.56 (dd, ^3J = 4.9, J = 1.6 Hz, 1H; C*H*, ar), 7.83 (ddd, ^3J = 7.9, J = 2.4, 1.6 Hz, 1H; C*H*, ar), 7.47 (d, ^3J = 8.2 Hz, 2H; C*H*, ar), 7.32 (ddd, ^3J = 7.9, J = 4.9, 0.7 Hz, 1H; C*H*, ar), 7.27 (d, ^3J = 7.9 Hz, 2H; C*H*, ar), 2.40 ppm (s, 3H; CH_3); ^{13}C{^{1}H} NMR (125.8 MHz, $CDCl_3$): δ = 147.2 (2 x), 137.0, 135.5, 133.9, 133.1, 128.8, 125.9, 122.4, 20.1 ppm; ^{15}N NMR (50.7 MHz, $CDCl_3$): δ = −68.1 ppm; HRMS: *m/z*: calcd for $C_{12}H_{11}N_1$: 169. 0892; found: 169.08751.

4-(2,6-Dimethylphenyl)pyridine (Table 5, entry 3): ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.67 (dd, ^3J = 4.4, J = 1.7 Hz, 2H; C*H*, ar), 7.20 (dd, ^3J = 8.2, 7.0 Hz, 1H; C*H*, ar), 7.12 (d, ^3J = 7.0 Hz, 2H; C*H*, ar), 7.11 (dd, ^3J = 4.4, J = 1.7 Hz, 2H; C*H*, ar), 2.02 ppm (s, 6H; CH_3); ^{13}C{^{1}H} NMR (125.8 MHz, $CDCl_3$): δ = 149.1, 148.4, 138.0, 134.1, 126.8, 126.6, 123.4, 19.6 ppm; ^{15}N NMR (50.7 MHz, $CDCl_3$): δ = −72.8 ppm; HRMS: *m/z*: calcd for $C_{13}H_{13}N_1$: 183.1048; found: 183.10352.

[3,3′]-Bipyridyl (Table 5, entry 4): ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.85 (dd, ^5J = 2.5, J = 1.0 Hz, 2H; C*H*, ar), 8.66 (dd, ^3J = 4.8, J = 1.5 Hz, 2H; C*H*, ar), 7.89 (ddd, ^3J = 8.0, J = 2.5, 1.8 Hz, 2H; C*H*, ar), 7.42 ppm (ddd, ^3J = 8.0, J = 4.8, J = 1.0 Hz, 2H; C*H*, ar); ^{13}C{^{1}H} NMR (125.8 MHz, $CDCl_3$): δ = 149.4, 148.2, 134.4, 133.5, 123.8 ppm; ^{15}N NMR (50.7 MHz, $CDCl_3$) δ = −66.4 ppm; HRMS: *m/z*: calcd for $C_{10}H_8N_2$: 156.0688; found: 156.06957.

[3,4′]-Bipyridyl (Table 5, entry 5): ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.90 (d, ^3J = 2.0 Hz, 1H; C*H*, ar), 8.72 (dd, ^3J = 4.5, J = 1.7 Hz, 2H; C*H*, ar), 8.69 (dd, ^3J = 4.9, J = 1.5 Hz, 1H; C*H*, ar), 7.93 (ddd, ^3J = 8.0, J = 2.4, 1.7 Hz, 1H; C*H*, ar), 7.51 (dd, ^3J = 4.5, J = 1.7 Hz, 2H; C*H*, ar), 7.43 ppm (ddd, ^3J = 8.0, 4.9, J = 0.7 Hz, 1H; C*H*, ar); ^{13}C{^{1}H} NMR (125.8 MHz, $CDCl_3$): δ = 150.6, 150.2, 148.2, 145.2, 134.3, 133.8, 123.8, 121.6 ppm; ^{15}N NMR (50.7 MHz, $CDCl_3$): δ = −66.5, −69.8 ppm; HRMS: *m/z*: calcd for $C_{10}H_8N_2$: 156.0688; found: 156.0679.

1-(3′-Methoxybiphenyl-4-yl)-1*H*-pyrrole (Table 5, entry 6): ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.62 (d, ^3J = 8.6 Hz, 2H; C*H*, ar), 7.43 (d, ^3J = 8.6 Hz, 2H; C*H*, ar), 7.35 (t, ^3J = 7.9 Hz, 1H; C*H*, ar), 7.17 (ddd, ^3J = 7.6, J = 1.6, 0.9 Hz, 1H; C*H*, ar), 7.13–7.10 (m, 3H; C*H*, ar), 6.90 (ddd, ^3J = 8.2, J = 2.6, 0.9 Hz, 1H; C*H*, ar), 6.36 (t, ^3J = 2.2 Hz, 2H; C*H*, ar), 3.85 ppm (s, 3H; OCH_3); ^{13}C{^{1}H} NMR (125.8 MHz, $CDCl_3$): δ = 160.1, 141.7, 140.0, 138.4, 129.9, 128.2, 120.6, 119.4, 119.3, 112.8, 112.7, 110.6, 55.3 ppm; ^{15}N NMR (50.7 MHz, $CDCl_3$): δ = − 206.7 ppm; HRMS: *m/z*: calcd for $C_{17}H_{15}N_1O_1$: 249.1154; found: 249.11369.

3-(4-Pyrrol-1-ylphenyl)pyridine (Table 5, entry 7): ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.86 (dd, ^3J = 2.5, J = 0.6 Hz, 1H; C*H*, ar), 8.60 (dd, ^3J = 4.8, J = 1.6 Hz, 1H; C*H*, ar), 7.86 (ddd, ^3J = 7.9, J = 2.5, 1.6 Hz, 1H; C*H*, ar), 7.62 (d, ^3J = 8.6 Hz, 2H; C*H*, ar), 7.49 (d, ^3J = 8.6 Hz, 2H; C*H*, ar), 7.36 (ddd, ^3J = 7.9, J = 4.9, J = 0.7 Hz, 1H; C*H*, ar), 7.13 (t, ^3J = 2.2 Hz, 2H; C*H*, ar), 6.38 ppm (t, ^3J = 2.2 Hz, 2H; C*H*, ar); ^{13}C{^{1}H} NMR (125.8 MHz, $CDCl_3$): δ = 147.6, 147.1, 139.6, 134.6, 134.0, 133.0, 127.2, 122.6, 119.8, 118.2, 109.8 ppm; ^{15}N NMR (50.7 MHz, $CDCl_3$): δ = − 66.8, −206.9 ppm; HRMS *m/z* calcd for $C_{15}H_{11}N_2$: 220.1001; found: 220.10105.

6-*p*-Tolyl-9*H*-purine (Table 6, entry 1): ^{1}H NMR (500 MHz, [D_6]DMSO): δ = 13.59 (brs, 1H; NH), 8.92 (s, 1H; ar (pos. 2)), 8.83–8.70 (brm, 2H; ar (*o*-tol)), 8.61 (s, 1H; ar (pos. 8)), 7.39 (d, ^3J = 8.0 Hz, 2H; ar (*m*-tol)), 2.40 ppm (s, 3H; CH_3); ^{13}C{^{1}H} NMR (125.75 MHz, [D_6]DMSO): δ = 153.7 (br), 152.5 (br), 152.2, 144.9 (br), 141.1, 133.3, 129.9 (br), 129.6 (4×), 21.4 ppm; ^{15}N NMR (50.69 MHz, [D_6]DMSO): δ = −223.1, −137.9, −130.3, −112.3 ppm; HRMS: *m/z*: calcd for $C_{12}H_{10}N_4$: 210.0906; found: 210.08788.

6-(3-Methoxyphenyl)-9*H*-purine (Table 6, entry 2): ^{1}H NMR (500 MHz, [D_6]DMSO): δ = 13.40 (brs, 1H; NH), 8.96 (s, 1H; ar (pos. 2)), 8.65 (s,

1H; ar (pos. 8)), 8.52–8.35 (brm, 2H; (*o*-anis), 7.50 (t, ^3J=8.2 Hz, 1H; ar (*m*-anis)), 7.14 (ddd, ^3J=8.2, J=2.5, 0.9 Hz, 1H; ar (*p*-anis)), 3.87 ppm (s, 3H; OCH_3); $^{13}C\{^1H\}$ NMR (125.75 MHz, [D$_6$]DMSO): δ=159.8, 154.1 (br), 152.1, 152.0 (br), 145.4 (br), 137.4, 130.2 (br), 130.0, 122.1, 117.0, 114.5, 55.5 ppm; ^{15}N NMR (50.69 MHz, [D$_6$]DMSO): δ=−222.8, −138.0, −128.3, −111.1 ppm; HRMS: *m/z*: calcd for $C_{12}H_{10}N_4O$: 226.0855; found: 226.08501.

3-Thiophen-2-ylpyridine (Table 7, entry 2): ^1H NMR (500 MHz, $CDCl_3$): δ=8.89 (s, 1H; C*H*, ar), 8.52 (d, J=3.5 Hz, 1H; C*H*, ar), 7.86 (dt, ^3J=8.0, J=1.6 Hz, 1H; C*H*, ar), 7.36 (s, 1H; C*H*, ar), 7.35 (q, J=1.3 Hz, 1H; C*H*, ar), 7.30 (dd, ^3J=7.6, J=4.8 Hz, 1H; C*H*, ar), 7.12 ppm (dd, ^3J=5.0, J=3.8 Hz, 1H; C*H*, ar); $^{13}C\{^1H\}$ NMR (125.77 MHz, $CDCl_3$): δ=147.4, 146.0, 139.3, 132.1, 129.5, 127.3, 125.1, 123.2, 122.6 ppm; HRMS: *m/z*: calcd for C_9H_7NS: 161.03; found: 161.02992.

2-Methyl-5-*p*-tolylbenzothiazole (Table 7, entry 3): ^1H NMR (500 MHz, $CDCl_3$): δ=8.15 (d, J=1.6 Hz, 1H; C*H*, ar), 7.84 (dd, ^3J=8.2, J=0.6 Hz, 1H; C*H*, ar), 7.56 (ddd, ^3J=10.0, 8.2, J=1.7 Hz, 1H; C*H*, ar), 7.55 (d, ^3J=8.0 Hz, 2H; C*H*, ar), 7.28 (dt, ^3J=7.9, J=0.6 Hz, 2H; C*H*, ar), 2.85 (s, 3H; SCCH_3), 2.41 ppm (s, 3H; CH_3-tolyl); $^{13}C\{^1H\}$ NMR (125.77 MHz, $CDCl_3$) δ=166.5, 153.1, 138.5, 136.9, 136.2, 133.3, 128.6, 126.2, 123.0, 120.4, 119.5, 20.1, 19.2 ppm; $^{15}N\{^1H\}$ NMR (50.69 MHz, $CDCl_3$): δ=−73.5 ppm; HRMS: *m/z*: calcd for $C_{15}H_{13}NS$: 239.0769; found: 239.07605.

2-Methyl-5-pyridin-3-ylbenzothiazole (Table 7, entry 4): ^1H NMR (500 MHz, $CDCl_3$): δ=8.93 (d, J=2.2 Hz, 1H; C*H*, ar), 8.62 (dd, ^3J=4.8, J=1.6 Hz, 1H; C*H*, ar), 8.16 (d, J=1.6 Hz, 1H; C*H*, ar), 7.94 (ddd, ^3J=7.9, J=2.2, J=1.6 Hz, 1H; C*H*, ar), 7.92 (d, ^3J=8.4 Hz, 1H; C*H*, ar), 7.57 (dd, ^3J=8.4, J=1.9 Hz, 1H; C*H*, ar), 7.40 (ddd, ^3J=7.9, J=4.8, J=0.8 Hz, 1H; C*H*, ar), 2.87 ppm (s, 3H; SCCH_3); $^{13}C\{^1H\}$ NMR (125.77 MHz, $CDCl_3$): δ=167.1, 153.2, 147.6, 147.5, 135.3, 135.0, 134.5, 133.5, 122.9, 122.6, 121.0, 119.8, 19.2 ppm; $^{15}N\{^1H\}$ NMR (50.69 MHz, $CDCl_3$): δ=−73.6, −67.2 ppm; HRMS: *m/z*: calcd for $C_{13}H_{10}N_2S$: 226.0566; found: 226.05647.

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4.6. Effiziente Suzuki-Miyaura-Kupplung von Arylchloriden mit Thiophen- und Furanboronsäuren in wässrigem n-Butanol

Der Inhalt dieses Kapitels wurde bereits veröffentlicht:

Christoph A. Fleckenstein, Herbert Plenio, *"Efficient Suzuki-Miyaura Coupling of (Hetero)aryl Chlorides with Thiophene- and Furanboronic Acids in Aqueous n-Butanol"*, *J. Org. Chem.* **2008**, *73*, 3236-3244.

In diesem Kapitel wird die Anwendung des in Kapitel 4.5. optimierten Suzuki-Kupplungsprotokolls in *n*-Butanol/Wasser als Reaktionsmedium für Thiophen- und Furanboronsäuren beschrieben. Es ist bekannt, dass Boronsäuren mit Thiophen oder Furan als Grundkörper instabiler als beispielsweise Phenylboronsäuren sind. In polar protischen Lösemitteln zerfallen sie rasch in einer Protodeboronierungsreaktion. Aufgrund der Instabilität der Boronsäuren sind nur wenige katalytische Systeme bekannt, die es vermögen, Heteroboronsäuren dieser Art zu kuppeln. Die wenigen anwendbaren Reaktionsprotokolle erzwingen in der Regel wasserfreie Reaktionsmedien, um hohe katalytische Aktivitäten und gute Umsätze zu erzielen.

Aufgrund der hohen Katalysatoraktivität von Pd-*cataCXium® FSulf* in wässrigem *n*-Butanol gelingt die Suzuki-Kupplung von Chloraromaten mit Thiophen- und Furanboronsäuren auch unter wässrigen Bedingungen unter Verwendung des optimierten Standardprotokolls aus Kapitel 4.5.. Unter diesen Bedingungen erfolgt die Kupplungsreaktion schneller als die konkurrierende Protodeboronierung.

Anhand von dreiundzwanzig Reaktionsbeispielen konnte die Robustheit des Verfahrens demonstriert werden. Die quantitative Kupplung diverser *N*-heterocyclischer und nichtheterocyclischer Chloraromaten mit Thiophen- und Furanboronsäuren war unter Einsatz von 0.1-1 mol% Katalysator zu erreichen. Im Vergleich mit wasserfreiem Reaktionsmedium erwies sich das verwendete *n*-Butanol/Wasser System mit dem Katalysator Pd-*cataCXium® FSulf* als signifikant aktiver. Darüber hinaus war eine höhere Produktselektivität durch Verwendung des wässrigen Systems im Vergleich zum wasserfreien System zu beobachten.

JOC Article

Efficient Suzuki−Miyaura Coupling of (Hetero)aryl Chlorides with Thiophene- and Furanboronic Acids in Aqueous *n*-Butanol

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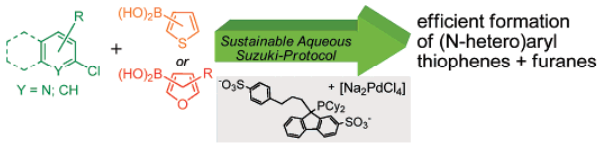

An efficient Suzuki cross-coupling protocol enables the reaction of *N*-hetero and normal aryl chlorides with thiophene- and furanboronic acids. Coupling is effected in aqueous *n*-butanol as the solvent in near quantitative yield with a catalyst loading of 0.1−1 mol %. For heterocyclic substrates aqueous catalysis is found to be more efficient than Suzuki coupling under anhydrous conditions. The developed Suzuki coupling procedure utilizes biodegradable solvents and is useful for large scale reactions, as it includes the facile product separation from a biphasic solvent mixture without the need for additional organic solvents during workup.

Introduction

Thiophenes are common in natural products and constitute attractive targets in pharmaceutical and fine chemistry because of their potential biological activity,[1−13] furans are found in numerous natural products,[14] flavors, and fragrances;[15,16] molecules bearing a furan moiety often display pharmacological activity.[13,17−21] (*N*-Hetero)arylthiophenes and -furans such as thiophenylpyridines,[11,22] furanylpyridines,[17] or furanylquinolines,[18] are ubiquitous in drugs.[19]

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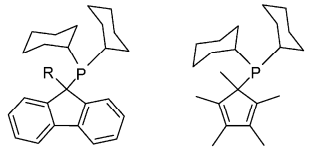
2-Arylated furans and thiophenes are accessible via conventional electrophilic substitution reactions[20] or CH-activation,[21] while the 3-position in thiophenes and furans is less easily accessible.[20,22] The Suzuki coupling[23,24] can be very useful for the synthesis of arylthiophenes or -furans. Such coupling reactions proceed smoothly only when halogenothiophenes or -furans are reacted with the respective aryl boronic acids. Typically catalyst loadings of 0.05−2.0 mol % tend to be sufficient for the quantitative coupling of chlorothiophenes or chlorofurans with sterically hindered boronic acids,[25,26] pyridylboronic acid,[27,28] or phenylboronic acid.[29] Quite in contrast, the use of thiophene- or furanboronic acids in Suzuki reactions is fraught with problems, because of the facile decomposition of such metalloids in polar protic reaction media via protodeboronation.[30−33] This was studied in detail by Roques et al. for furanboronic acids[34] and by Brown et al. for thiopheneboronic acids.[35] Consequently, the general application of such thiophene and furan metalloids is limited to the use of aryl iodides/bromides or activated aryl chlorides as coupling partners.[36−39] With thiopheneboronic acid, the more challenging 2-chloropyridine or related compounds are problematic[40] and require high catalyst loadings (1−10 mol %) for activated *N*-heterocyclic aryl chlorides.[25,41,42] The Suzuki coupling of furanboronic acid has primarily been explored in combination with iodo- and bromo(hetero)aryl halides;[18,39,43,44] only few examples are known for the conversion of activated *N*-heteroaryl chlorides.[45,46] Notable exceptions are efficient catalysts recently reported by Buchwald and Billingsley; the Suzuki protocol developed by Buchwald proved to be efficient for the coupling of various furanboronic acids with activated aryl chlorides but failed with *N*-heterocyclic chlorides.[27] Only a few examples are known for the coupling of less activated[47−49] or (hetero)aryl chlorides[50] with furanboronic acids. Trifluoroborates can be alternatives to the classical boronic acids. However the corresponding thiophene- and furan metalloids also suffer from low stability; thus, efficient Suzuki reactions are facile only with aryl bromides. Only few transformations of aryl chlorides were reported.[51]

SCHEME 1. Ligands Tested in Suzuki Cross-Coupling of Thiopheneboronic Acids



1 (R = benzyl)
2 (R = ethyl)
3 (R = 3-phenylpropyl)

4

The limitations in Suzuki couplings with thiophene- and furanboronic acids result from the dichotomy that polar protic solvents are known to facilitate this kind of catalytic reaction, while boronic acids tend to be unstable in these solvents. Hence, in order to improve the efficiency of Suzuki couplings with these heteroarylboronic acids, coupling catalysts need to be developed, which accelerate the respective cross-coupling reactions such that it turns out to be significantly faster than the competitive protodeboronation in polar protic solvents.

On the basis of our recent development of the cataCXium F family of fluorenylphosphines,[52−54] we report here on Pd-phosphine complex catalysts, which enable the efficient coupling of thiophene- and furanboronic acids in anhydrous and in aqueous media.

Results and Discussion

Suzuki Coupling, with Thiopheneboronic Acids under Anhydrous Conditions. Pd complexes of fluorenyldialkylphosphines constitute highly active catalysts for Suzuki coupling, especially for *N*-heterocyclic compounds.[28,55] The ligands depicted in Scheme 1 were the most useful ones in various cross-coupling reactions. Consequently, we decided to first evaluate these ligands in the anhydrous Suzuki coupling with thiophene- and furanboronic acids. In a preliminary study we tested three fluorenylphosphines (**1**−**3**) and Cp*PCy_2 (**4**). 2-Chloropyridine

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(47) Bracher, F.; Hildebrand, D. *Liebigs Ann. Chem.* **1992**, *12*, 1315−1319.
(48) Schirok, H. *J. Org. Chem.* **2006**, *71*, 5538−5545.
(49) Allegretti, M.; Arcadi, A.; Marinelli, F.; Nicolini, L. *Synlett* **2001**, *5*, 609−612.
(50) Li, J.-H.; Deng, C.-L.; Xie, Y.-X. *Synth. Commun.* **2007**, *37*, 2433−2448.
(51) Molander, G. A.; Biolatto, B. *J. Org. Chem.* **2003**, *68*, 4302 -4314.
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(53) Fleckenstein, C. A.; Plenio, H. *Organometallics* **2007**, *26*, 2758−2767.
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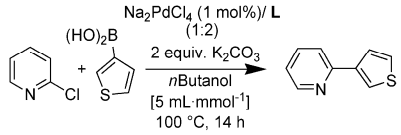
(55) Fleckenstein, C. A.; Plenio, H. *Green Chem.* **2007**, *9*, 1287−1291.

TABLE 1. Catalytic Activity of Various Pd-Phosphine Complexes in the Suzuki Cross-Coupling of Thiopheneboronic Acids



entry	ligand **L**	yield[a] (%)
1	**1**	66
2	**2**	≥99
3	**3**	68
4	**4**	86

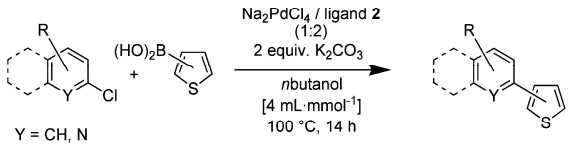
[a] Average of two runs, determined by GC using heptadecane as internal standard.

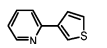
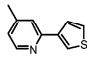
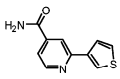
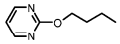
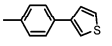
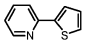
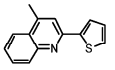
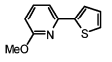
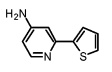
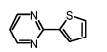
was reacted with 3-thiopheneboronic acid using anhydrous *n*-butanol as the solvent and a 1 mol % catalyst loading.

Of these phosphines the *in situ* formed [Pd/**2**] complex (**2** = 9-(9′-ethylfluorenyl)dicyclohexylphosphine) was the most effective one in the coupling of 2-chloropyridine with 3-thiopheneboronic acid (Table 1).

Consequently we studied complex [Pd/**2**] in more detail for Suzuki cross-coupling of 2- and 3-thiopheneboronic acids. Because of its higher stability, 3-thiopheneboronic acid allows lower catalyst loadings for quantitative Suzuki cross-coupling. Applying 0.1 mol % [Pd/**2**]-complex as catalyst, 2-chloropyridine was successfully cross-coupled with 3-thiopheneboronic acid in pure *n*-butanol at 100 °C using K_2CO_3 as base with an 89% conversion. Quantitative conversion was accomplished at 0.5 mol % catalyst loading (Table 2, entry 1). In the same manner 2-chloro-4-picoline and 2-chloro-isonicotinamide were reacted with 3-thiopheneboronic acid affording near quantitative

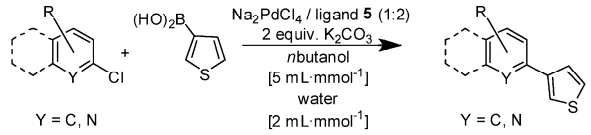
TABLE 2. Suzuki Reaction with 3- and 2-Thiopheneboronic Acid Utilizing Anhydrous *n*-Butanol Reaction Media[a]

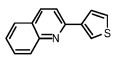
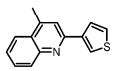
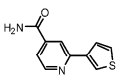
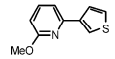
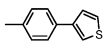


Entry	Aryl Chloride	Boronic Acid	Product	Pd [mol %]	Conversion[b] [%]	Yield[c] [%]
1				0.1 0.5	89 ≥99	93
2				0.5	≥99	89
3				0.5	≥99	91
4				0.5	≥99	79
5				1	98	93
6				1	≥99	91[d]
7				1	73	51[d]
8				1	17	[d], [e]
9				1	<5	0[d]
10				0.5	≥99	89[d]

[a] Reaction conditions: 1.0 equiv of aryl halide, 1.5 equiv of boronic acid, 3.2 equiv of K_2CO_3, 100 °C, 14 h, cat.: the respective volume of catalyst stock solution (in *n*-butanol) (c_{Pd} = 0.01 mol/L, Na_2PdCl_4/ligand **2** L/Pd = 2:1). Reaction times and temperature were not optimized. [b] Average of two runs, determined by GC using heptadecane as internal standard. [c] Average of two runs, products were isolated via column chromatography (silica (20 × 3 cm), cyclohexane:EtOAc:NEt_3 (10:1:1) as eluent). [d] Degassed *tert*-amyl alcohol (5 mL $mmol^{-1}$) in addition to 0.25 g of molecular sieves 4 Å was used instead *n*-butanol of as reaction solvent and for *in situ* preparation of the precatalyst. [e] Product not isolated.

TABLE 3. Suzuki Reaction with 3-Thiopheneboronic Acid Using *n*-Butanol/Water as Solvent[a]



Entry	Aryl Chloride	Boronic Acid	Product	Pd [mol %]	Conversion[b] [%]	Yield[c] [%]
1				0.1	>99	90
2				0.25	≥99	95
3				0.25	≥99	91
4				0.25	≥99	93
5				0.25	≥99	93
6				0.25	≥99	95
7				0.1	≥99	95
8				1.0 0.5	≥99 83	92

[a] Reaction conditions: 1.0 equiv of aryl halide, 1.5 equiv of boronic acid, 3.2 equiv of K_2CO_3, degassed *n*-butanol (5 mL mmol^{-1}), degassed water (2 mL·mmol^{-1}), 100 °C, 12 h, cat.: the respective volume of catalyst stock solution (in *n*-butanol) (c_{Pd} = 0.005 mol/L, Na_2PdCl_4/ligand **5** L/Pd = 2:1). Reaction times and temperature were not optimized. [b] Average of two runs, determined by GC using heptadecane as internal standard. [c] Average of two runs, products were isolated via column chromatography (silica (20 × 3 cm), cyclohexane:EtOAc:NEt_3 (10:1:1) as eluent).

yield (89%, 91%) at 0.5 mol % catalyst loading (Table 2, entries 2 + 3). 4-Chlorotoluene is coupled with the same metalloid quantitatively using 1 mol % catalyst (Table 2, entry 5). Interestingly, when *n*-butanol was used as a solvent, the highly active 2-chloropyrimidine preferably underwent an S_NAr-mechanism instead of the slower Suzuki cross-coupling reaction to form the undesired product 2-butoxypyrimidine in 79% yield (Table 2, entry 4).[56] Consequently, we switched to *tert*-amyl alcohol under anhydrous conditions (in combination with molecular sieves) as solvent with the more labile 2-thiopheneboronic acid. Then the activated 2-chloropyrimidine reacted smoothly and selectively with 2-thiopheneboronic acid in *tert*-amyl alcohol as solvent, affording 89% isolated yield with 0.5 mol % catalyst loading (Table 2, entry 10). Under these conditions, formation of the respective ether was not detected. When 1 mol % catalyst loading was applied, 2-chloropyridine was quantitatively cross-coupled with 2-thiopheneboronic acid using *tert*-amyl alcohol as solvent (Table 2, entry 6). However more deactivated *N*-heterocyclic aryl chlorides like 2-chlorolepidine or 2-chloro-6-methoxypyridine were not quantitatively Suzuki cross-coupled using 1 mol % [Pd/**2**]-complex as catalyst (Table 2, entries 7 + 8, 73% and 17% conversion, respectively).

(56) 2-Butoxypyrimidine is also formed in the absence of catalyst under otherwise identical reaction conditions.

Unfortunately, the catalyst failed with the most challenging substrate combination of 4-amino-2-chloropyridine and 2-thiopheneboronic acid (Table 2, entry 9).

In conclusion, the fluorenylphosphine-based catalysts show activity comparable to the best systems reported so far for Suzuki coupling of aryl chlorides with thiopheneboronic acids.[27]

Suzuki Coupling Using an Aqueous Reaction Protocol. Very recently we reported that water as a (co)solvent drastically enhances the Suzuki coupling of *N*-heterocyclic substrates.[28,55,57,58] In this context, the use of Pd complexes with highly water soluble disulfonated fluorenyldialkylphosphine **5** (Scheme 2)[59] led to unprecedented activities in the Suzuki coupling of heteroaryl chlorides. According to our hypothesis, the nitrogen moieties of the applied substrates preferentially engage in hydrogen bonding[60] with water rather than coordinating to the Pd-center of the active catalyst. In this manner poisoning of the catalyst by the heterocyclic substrates[39] is minimized.

We were interested to learn whether enhanced Suzuki

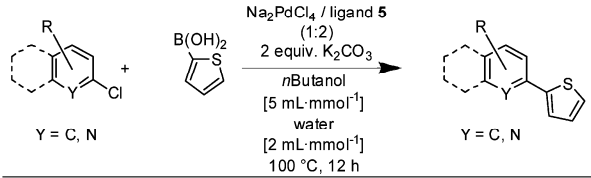
(57) Fleckenstein, C. A.; Roy, S.; Leuthäusser, S.; Plenio, H. *Chem. Commun.* **2007**, 2870−2872.

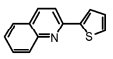
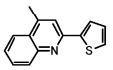
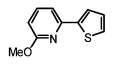
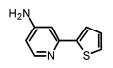
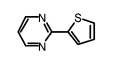
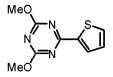
(58) an der Heiden, M. R.; Plenio, H. *Chem. Eur. J.* **2004**, *10*, 1789−1797.

(59) This ligand is commercially available from Strem and Aldrich under the trade name cataCXium F Sulf.

(60) Plenio, H.; Diodone, R. *Chem. Ber.* **1997**, *130*, 633−640.

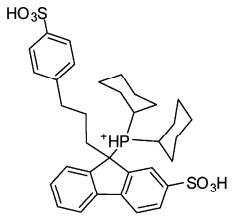
TABLE 4. Suzuki Reaction with 2-Thiopheneboronic Acid Using *n*-Butanol/Water as Solvent[a]



Entry	Aryl Chloride	Boronic Acid	Product	Pd [mol %]	Conversion[b] [%]	Yield[c] [%]
1				1	≥99	90
2				1	≥99	94
3				1	≥99	95
4				1	31	31[b,d]
5				1	6	6[b,d]
6				0.5	≥99	94
7				0.5	98	89

[a] Reaction conditions: 1.0 equiv of aryl halide, 1.5 equiv of boronic acid, 3.2 equiv of K_2CO_3, degassed *n*-butanol (5 mL mmol^{-1}), degassed water (2 mL·mmol^{-1}), 100 °C, 12 h, cat.: the respective volume of catalyst stock solution (in *n*-butanol) (c_{Pd} = 0.005 mol/L, Na_2PdCl_4/ligand **5** L/Pd = 2:1). Reaction times and temperature were not optimized. [b] Average of two runs, determined by GC using heptadecane as internal standard. [c] Average of two runs, products were isolated via column-chromatography (silica (20 × 3 cm), cyclohexane:EtOAc:NEt_3 (10:1:1) as eluent). [d] Product not isolated.

SCHEME 2. High Water Soluble Disulfonated Dicyclohexylfluorenylphosphine Ligand 5·3H$^+$



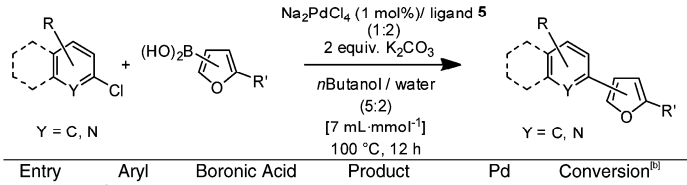
5 ·3 H$^+$

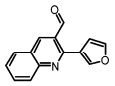
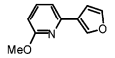
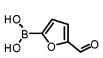
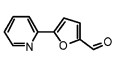
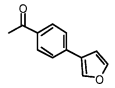
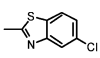
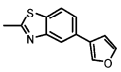
reactivity in water/*n*-butanol mixtures can be realized with labile thiophene- and furanboronic acids. This approach boldly ignores the fact that the decomposition of the thiophene- and furanboronic acids in water is drastically accelerated. On the other hand, the chosen aqueous/organic reaction medium is convenient as it is cheap, safe, and biodegradable. We were pleased to see, that in a preliminary test with Pd/**5** as catalyst (formed *in situ* from Na_2PdCl_4 and the phosphonium salt of **5**), 2-chloropyridine was smoothly coupled with 3-thiopheneboronic acid in water/*n*-butanol (2:5) as solvent and K_2CO_3 as base at 100 °C utilizing only 0.1 mol % catalyst (Table 3, entry 1). This indicates that the aqueous reaction protocol is superior to the anhydrous one, which requires a fivefold higher catalyst loading to achieve full conversion (see Table 2, entry 1; 0.5 mol %). In order to substantiate the robustness of the aqueous cross-coupling protocol, we coupled a variety of *N*-heterocyclic and normal aryl chlorides with 2-thiophene- and 3-thiopheneboronic acids.

Suzuki Coupling of 3-Thiopheneboronic Acid. Utilizing a catalyst loading of 0.25 mol % a number of activated and deactivated chloropyridines and chloroquinolines were quantitatively Suzuki coupled with 3-thiopheneboronic acid in water/*n*-butanol as solvent (Table 3, entries 2−6). This reaction protocol enables efficient coupling of 4-chlorotoluene with 3-thiopheneboronic acid affording 83% conversion at a catalyst loading of 0.5 mol % and quantitative coupling applying 1 mol % catalyst, respectively (Table 3, entry 8). The reaction of 2-chloropyrimidine with 3-thiopheneboronic acid using 0.1 mol % catalyst selectively and quantitatively affords the desired Suzuki biaryl in water/*n*-butanol as solvent. The formation of 2-*n*-butoxypyrimidine, which was isolated as main product when working under anhydrous conditions, was not observed. Obviously, the use of water effectively inhibits the undesired ether formation.

Suzuki Coupling of 2-Thiopheneboronic Acid. Suzuki coupling of 2-thiopheneboronic acids required higher catalyst loadings because of the increased propensity of this metalloid toward protodeboronation, which is about 120 times faster than that of 3-thiopheneboronic acid.[35] When 1 mol % of Pd/**5** was applied, the substrates 2-chloropyridine, 2-chloroquinoline, and 2-chlorolepidine were smoothly coupled with this heteroboronic

TABLE 5. Suzuki Reaction with Furanboronic Acids Using *n*-Butanol/Water as Solvent[a]



Entry	Aryl Chloride	Boronic Acid	Product	Pd [mol %]	Conversion[b] [%]	Yield[c] [%]
1				1	≥99	93
2				1	≥99	97
3				1	≥99	96
4				1	≥99	92
5				1	≥99	93
6				1	94	90
7				1	≥99	95
8				1	≥99	97

[a] Reaction conditions: 1.0 equiv of aryl halide, 1.5 equiv of boronic acid, 3.2 equiv of K_2CO_3, degassed *n*-butanol (5 mL $mmol^{-1}$), degassed water (2 $mL \cdot mmol^{-1}$), 100 °C, 12 h, cat.: the respective volume of catalyst stock solution (in *n*-butanol) (c_{Pd} = 0.005 mol/L, Na_2PdCl_4/ligand **5** L/Pd = 2:1). Reaction times and temperature were not optimized. [b] Average of two runs, determined by GC using heptadecane as internal standard. [c] Average of two runs, products were isolated via column chromatography (silica (20 × 3 cm), cyclohexane:EtOAc:NEt_3 (10:1:1) as eluent). [d] Product not isolated.

acid (Table 4, entries 1−3). Again the aqueous coupling protocol demonstrates its superiority over the anhydrous protocol where full conversion of 2-chlorolepidine with 2-thiopheneboronic acid was not feasible using Pd/**2** at the same catalyst-loading (Table 2, entry 7, 73% conversion); such limitations in the conversion of *N*-heteroaryl chlorides were also reported in the Buchwald protocol.[27] Nonetheless, deactivated *N*-heterocyclic aryl chlorides did not undergo full conversion under aqueous conditions but still performed significantly better than under anhydrous conditions (Table 4, entries 4, 5). Pharmaceutically interesting chloroazines like 2-chloropyrimidine and 2-chloro-3,5-dimethoxytriazine (another biological active moiety)[61,62] are smoothly coupled with 2-thiopheneboronic acid using the aqueous reaction conditions, affording 94% and 89% isolated yield, respectively, with 0.5 mol % catalyst loading (Table 4, entries 6 + 7). Formation of undesired *N*-arylbutoxide byproducts was not observed.

Suzuki Coupling of Furanboronic Acids. Next we studied the applicability of our aqueous reaction protocol to the coupling of the more labile furanboronic acids. We were pleased to observe the smooth coupling of 3-furanboronic acid with a large variety of activated and deactivated 2-chloropyridines and 2-chloroquinolines and 2-chloropyrimidine including the notorious 4-amino-2-chloropyridine (typically 92−97% yield, 1 mol % Pd/**5**) (Table 5, entries 1−5). Suzuki coupling with 3-furanboronic acid is not limited to *N*-heteroaryl chlorides: *p*-chloroacetophenone or 6-chloro-5-methylbenzothiazole are arylated using the same conditions as for the heteroaryl chlorides (Table 5, entries 7 and 8). Thus, the reactivity of this catalytic system is significantly higher than that of other protocols which are limited to activated (*N*-hetero)aryl chlorides.[27] Our aqueous reaction protocol enables Suzuki coupling of electron-deficient and thus more labile 2-furanboronic acids. Unfortunately, the rapid decomposition of 2-furanboronic acids still prevents coupling of nonactivated aryl chlorides.

Other than providing high Suzuki reactivity, the developed reaction protocol is very convenient in many respects: (a) the water/*n*-butanol mixture is cheap and nontoxic, and the organic component is biodegradable; (b) anhydrous conditions are not required; (c) a convenient base (K_2CO_3) is used. When working on larger scale, product separation is simple since additional organic solvents such as ethers or alkanes are not required.

(61) Dianzani, C.; Collino, M.; Gallicchio, M.; Samaritani, S.; Signore, G.; Menicagli, R.; Fantozzi, R. *J. Pharm. Pharmacol.* **2006**, *58*, 219−226.
(62) Menicagli, R.; Samaritani, S.; Signore, G.; Vaglini, F.; Via, L. D. *J. Med. Chem.* **2004**, *47*, 4649−4652.

Instead, addition of more water to the reaction mixture ensures an effective separation of the product-containing *n*-butanol layer from the water layer containing salts as well as excess of boronic acid. In cases of quantitative conversion of the aryl chloride, simple phase separation, drying of the alcoholic solution, and solvent removal afforded the desired product in excellent isolated yield and high purity (>95% judged by GC and NMR) without additional chromatographic purification.

Summary and Conclusion

In summary, we have developed a highly efficient Suzuki cross-coupling protocol enabling conversion of *N*-hetero- and normal aryl chlorides with thiophene- and furanboronic acids in aqueous *n*-butanol as the solvent. The facile coupling reactions are based on the Pd complex of the highly water soluble disulfonated fluorenylphosphine **5**, obtained *in situ* from Na_2PdCl_4 and the respective phosphonium salt of **5**. For heterocyclic substrates, aqueous catalysis was found to be significantly more efficient than Suzuki coupling under anhydrous conditions. Using the aqueous catalysis protocol, a variety of different *N*-heterocyclic and nonheterocyclic aryl chlorides was Suzuki coupled with 2- and 3-thiopheneboronic acids as well as furanboronic acids in near quantitative yield at catalyst loadings of 0.1−1 mol %. The undesired ether formation observed for some substrate combinations in anhydrous *n*-butanol as the solvent is suppressed in the presence of water. Furthermore, on a large scale the developed system enables efficient and sustainable Suzuki coupling including the facile product separation without the need for additional organic solvents during workup.

Experimental Section

All chemicals were purchased as reagent grade from commercial suppliers and used without further purification, unless otherwise noted. Used solvents (water, *n*-butanol were all technical grade) were deaerated via freeze and thaw technique (2×). For cross-coupling reactions under anhydrous conditions, *n*-butanol (technical grade, dried over molecular sieves, 4 Å) was used. Potassium carbonate, used in cross-coupling reactions, was technical grade. The phosphine ligands were prepared according to published procedures: **1**,[54] **2**,[52] **3**,[54] **4**,[53] **5**;[28] these ligands are also commercially available under the trade name cataCXium F from Evonik-Degussa GmbH. All "phosphines" mentioned in this publication were used in the form of their air stable phosphonium salts and deprotonated *in situ* during the catalyst preparation. All experiments were carried out under an argon atmosphere, unless otherwise noted. Proton (^{1}H NMR), carbon (^{13}C NMR), phosphorus (^{31}P NMR), and nitrogen (^{15}N NMR) nuclear magnetic resonance spectra were recorded on Bruker DRX 500 at 500 MHz, 125.75, 202.46, and 50.69 MHz, respectively, at 293 K. The chemical shifts are given in parts per million (ppm) on the delta scale (δ) and are referenced to tetramethylsilane (δ = 0 ppm), ^{1}H NMR, 65% aq H_3PO_4. (δ = 0 ppm), ^{31}P NMR and nitromethane (δ = 0 ppm), ^{15}N NMR. Abbreviations for NMR data: s = singlet; d = doublet; t = triplet; q = quartet; qi = quintet; dd = doublet of doublets; dt = doublet of triplets; dq = doublet of quartets; tt = triplet of triplets; m = multiplet. Mass spectra were recorded on a Finnigan MAT 95 magnetic sector spectrometer. Thin layer chromatography (TLC) was performed using Fluka silica gel 60 F 254 (0.2 mm) on aluminum plates. Silica gel columns for chromatography were prepared with E. Merck silica gel 60 (0.063−0.20 mesh ASTM). GC experiments were run on a Clarus 500 GC with autosampler and FID detector. Column: Varian CP-Sil 8 CB (l = 15 m, diam = 0.25 mm, d_F = 1.0 μm), N_2 (flow: 17 cm/s; split 1:50); injector temperature: 270 °C, detector temperature: 350 °C. Temperature program: isotherm 150 °C for 5 min, heating to 300 °C with 25 °C/min, isotherm for 15 min.

General Procedures for the Suzuki Cross-Coupling Reactions. Preparation of Catalyst Stock Solution for Suzuki Coupling in Anhydrous Alcohols. [Na_2PdCl_4] (11.8 mg, 0.04 mmol), the respective phosphine (**1**−**4**) (0.08 mmol), and K_2CO_3 (69 mg, 0.5 mmol) were placed in a 10 mL Schlenk tube, evacuated, and backfilled with Ar thrice. Degassed dry *n*-butanol (4 mL) was added and the mixture stirred at 55 °C for 3 h to obtain a yellow suspension. c_{Pd} of this catalyst stock solution is 0.01 mmol·mL^{-1}. When the cross-coupling reaction was performed in *tert*-amyl alcohol as solvent, this alcohol was used for the stock solution.

Cross-Coupling Reaction in Anhydrous Alcohols (*n*-butanol or *tert*-amyl alcohol) as Solvent. Boronic acid (1.2 mmol) and K_2CO_3 (440 mg, 3.2 mmol) were placed in a 25 mL Schlenk tube, evacuated, and backfilled with Ar thrice. For cross-coupling reactions with 2-thiopheneboronic acids more molecular sieve (0.25, g 4 Å) was added prior to the degassing sequence. Then degassed *n*-butanol (or *tert*-amyl alcohol, respectively) (5 mL), the aryl halide (1 mmol), and the respective volume of catalyst stock solution were added. The reaction mixture was stirred for 12 h at 100 °C and then cooled to room temperature. Water (5 mL) was added, and the product was extracted with methyl *tert*-butyl ether (2 × 5 mL). The organic layer was concentrated *in vacuo* and the residue purified via column chromatography (silica (20 × 3 cm), cyclohexane:EtOAc:NEt_3 (10:1:1)), to afford the pure cross-coupling product in 51−93% yield, respectively.

Preparation of Catalyst Stock Solution for Suzuki Coupling in Aqueous *n*-Butanol. [Na_2PdCl_4] (5.9 mg, 0.02 mmol), phosphine **5** (30 mg, 0.04 mmol), and K_2CO_3 (33 mg, 0.24 mmol) were placed in a 25 mL Schlenk tube, evacuated, and backfilled with Ar thrice. Degassed water (4 mL) was added and the mixture stirred at 55 °C for 3 h to obtain a clear, nearly colorless solution. c_{Pd} of this catalyst stock solution is 0.005 mmol·mL^{-1}.

Cross-Coupling Reaction in Water/*n*-Butanol (screening experiments). Boronic acid (1.2 mmol) and K_2CO_3 (440 mg, 3.2 mmol) were placed in a 25 mL Schlenk tube, evacuated, and backfilled with Ar thrice. Then degassed *n*-butanol (5 mL) was added as well as the aryl halide (1 mmol) and the respective volume of catalyst stock solution. The amount of water in the reaction mixture was adjusted to 2 mL total volume. The reaction mixture was stirred for 12 h at 100 °C and then cooled to room temperature. Water (5 mL) was added, and the product was extracted with methyl *tert*-butyl ether (2 × 5 mL). The organic layer was concentrated *in vacuo* and the residue purified via column chromatography (silica (20 × 3 cm), cyclohexane:EtOAc:NEt_3 (10:1:1)) to afford the pure respective cross-coupling product in 89−97% yield.

Preparative Scale Cross-Coupling Reaction in Water/*n*-Butanol. 3-Thiopheneboronic acid (1.66 g, 13 mmol), 2-chloroquinoline (1.66 g, 10 mmol), and K_2CO_3(4.14 g, 30 mmol) were placed in a 50 mL Schlenk flask, evacuated, and backfilled with Ar thrice. Then degassed *n*-butanol (25 mL) was added as well as the catalyst stock solution (0.5 mol % catalyst loading). After the reaction mixture was stirred for 12 h at 100 °C, quantitative conversion was observed via GC chromatography. The reaction mixture was then cooled to room temperature, water (10 mL) was added, and the organic layer separated, dried over $MgSO_4$, and filtered. Removal of the volatiles *in vacuo* afforded the crude product 2-thiophen-3-ylquinoline (1.92 g, 91%) as an off white solid (purity checked by GC and ^{1}H NMR: >95%).

2-Thiophen-3-ylpyridine (Table 2, entry 1/Table 3, entry 1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.61 (dq, ^3J = 4.7 Hz, J = 1.0 Hz, 1 H, C*H*, ar), 7.89 (dd, ^3J = 3.2 Hz, J = 1.3 Hz, 1 H, C*H*, ar), 7.69−7.64 (m, 2 H, C*H*, ar), 7.59 (dt, ^3J = 8.0 Hz, J = 1.0 Hz, 1 H, C*H*, ar), 7.38 (dd, ^3J = 5.0 Hz, J = 3.0 Hz, 1 H, C*H*, ar), 7.14 (ddd, ^3J = 7.6 Hz, J = 4.6 Hz, J = 1.2 Hz, 1 H, C*H*, ar); ^{13}C{^{1}H}

NMR (125.77 MHz, $CDCl_3$) δ 154.0, 150.0, 142.6, 137.1, 126.7, 126.6, 123.9, 122.2, 120.7; HRMS calcd for C_9H_7NS: 161.03, found 161.02985.

2-Thiophen-3-ylquinoline (Table 3, entry 2). ^1H NMR (500 MHz, $CDCl_3$) δ 8.13 (d, ^3J = 8.5 Hz, 1 H, C*H*, ar), 8.11 (d, ^3J = 8.8 Hz, 1 H, C*H*, ar), 8.03 (dd, J = 3.0 Hz, J = 1.3 Hz, 1 H, C*H*, ar), 7.87 (dd, ^3J = 5.1 Hz, J = 1.3 Hz, 1 H, C*H*, ar), 7.77 (dd, ^3J = 8.0 Hz, J = 1.0 Hz, 1 H, C*H*, ar), 7.75 (d, ^3J = 8.6 Hz, 1 H, C*H*, ar), 7.69 (ddd, ^3J = 8.5 Hz, ^3J = 7.0 Hz, J = 1.5 Hz, 1 H, C*H*, ar), 7.49 (ddd, ^3J = 8.2 Hz, ^3J = 7.0 Hz, J = 1.3 Hz, 1 H, C*H*, ar), 7.43 (dd, ^3J = 5.0 Hz, J = 3.0 Hz, 1 H, C*H*, ar); $^{13}C\{^1H\}$ NMR (125.77 MHz, $CDCl_3$) δ 153.7, 148.7, 143.1, 137.1, 130.1, 129.9, 127.9, 127.5, 127.3, 126.8, 126.5, 125.0, 119.4; HRMS calcd for $C_{13}H_9NS$: 211.0456, found 211.04371.

4-Methyl-2-thiophen-3-ylpyridine (Table 2, entry 2/Table 3, entry 3). ^1H NMR (500 MHz, $CDCl_3$) δ 8.46 (d, ^3J = 5.0 Hz, 1 H, C*H*, ar), 7.87 (dd, ^3J = 2.9 Hz, J = 1.3 Hz, 1 H, C*H*, ar), 7.64 (dd, ^3J = 5.0 Hz, J = 1.2 Hz, 1 H, C*H*, ar), 7.43–7.41 (m, 1 H, C*H*, ar), 7.37 (dd, ^3J = 5.0 Hz, J = 2.8 Hz, 1 H, C*H*, ar), 6.97 (dq, ^3J = 5.0 Hz, J = 0.8 Hz, 1 H, C*H*, ar), 2.36 (s, 3 H, CH_3); $^{13}C\{^1H\}$ NMR (125.77 MHz, $CDCl_3$) δ 153.4, 149.4, 147.7, 142.3, 126.2, 126.2, 123.3, 122.9, 121.2, 21.1; HRMS calcd for $C_{10}H_9NS$: 175.0456, found 175.04453.

4-Methyl-2-thiophen-3-ylquinoline (Table 3, entry 4). ^1H NMR (500 MHz, $CDCl_3$) δ 8.10 (dq, ^3J = 8.5 Hz, J = 0.6 Hz, 1 H, C*H*, ar), 7.99 (dd, J = 1.2 Hz, J = 3.0 Hz, 1 H, C*H*, ar), 7.90 (dd, ^3J = 8.5 Hz, J = 1.2 Hz, 1 H, C*H*, ar), 7.84 (dd, ^3J = 5.1 Hz, J = 1.3 Hz, 1 H, C*H*, ar), 7.66 (ddd, ^3J = 8.5 Hz, ^3J = 7.0 Hz, J = 1.5 Hz, 1 H, C*H*, ar), 7.55 (d, J = 1.0 Hz, 1 H, C*H*, ar), 7.47 (ddd, ^3J = 8.5 Hz, ^3J = 7.0 Hz, J = 1.2 Hz, 1 H, C*H*, ar), 7.39 (dd, ^3J = 5.0 Hz, J = 3.0 Hz, 1 H, C*H*, ar), 2.67 (d, J = 1.0 Hz, 3 H, CH_3); $^{13}C\{^1H\}$ NMR (125.77 MHz, $CDCl_3$) δ 153.4, 148.5, 145.1, 143.2, 130.5, 129.7, 127.6, 127.3, 126.6, 126.2, 124.8, 124.0, 120.1, 19.3; HRMS calcd for $C_{14}H_{11}NS$: 225.0613, found 225.05940.

2-Thiophen-3-ylisonicotinamide (Table 2, entry 3/Table 3, entry 5). ^1H NMR (500 MHz, $DMSO_{d6}$) δ 8.71 (dd, ^3J = 5.0 Hz, J = 0.6 Hz, 1 H, C*H*, ar), 8.28 (s (br), 1 H, NH_2), 8.25–8.23 (m, 2 H, C*H*, ar), 7.80 (dd, ^3J = 5.0 Hz, J = 1.3 Hz, 1 H, C*H*, ar), 7.76 (s (br), 1 H, NH_2), 7.67 (dd, ^3J = 5.0 Hz, J = 3.2 Hz, 1 H, C*H*, ar), 7.65 (dd, ^3J = 5.0 Hz, J = 1.6 Hz, 1 H, C*H*, ar); $^{13}C\{^1H\}$ NMR (125.77 MHz, $DMSO_{d6}$) δ 166.7, 153.8, 150.5, 142.7, 141.9, 127.6, 126.6, 125.0, 120.1, 118.1; ^{15}N NMR (50.69 MHz, $DMSO_{d6}$) δ −275.1 (NH_2), −66.5 (pyridyl); HRMS calcd for $C_{10}H_8N_2OS$: 204.0358, found 204.03597.

2-Methoxy-6-thiophen-3-ylpyridine (Table 3, entry 6). ^1H NMR (500 MHz, $CDCl_3$) δ 7.90 (dd, J = 3.0 Hz, J = 1.2 Hz, 1 H, C*H*, ar), 7.63 (dd, ^3J = 5.0 Hz, J = 1.2 Hz, 1 H, C*H*, ar), 7.55 (dd, ^3J = 8.2 Hz, ^3J = 7.4 Hz, 1 H, C*H*, ar), 7.35 (dd, ^3J = 5.0 Hz, J = 3.0 Hz, 1 H, C*H*, ar), 7.17 (dd, ^3J = 7.5 Hz, J = 0.5 Hz, 1 H, C*H*, ar), 6.62 (dd, ^3J = 8.0 Hz, J = 0.5 Hz, 1 H, C*H*, ar), 4.00 (s, 3 H, OCH_3); $^{13}C\{^1H\}$ NMR (125.77 MHz, $CDCl_3$) δ 164.1, 151.4, 142.6, 139.5, 126.6, 126.4, 123.7, 113.0, 109.3, 53.6; HRMS calcd for $C_{10}H_9NOS$: 191.0405, found 191.04062.

2-Thiophen-3-ylpyrimidine (Table 3, entry 7). ^1H NMR (500 MHz, $CDCl_3$) δ 8.73 (d, ^3J = 5.0 Hz, 2 H, C*H*, ar), 8.30 (dd, J = 3.1 Hz, J = 1.2 Hz, 1 H, C*H*, ar), 7.90 (dd, ^3J = 5.0 Hz, J = 1.2 Hz, 1 H, C*H*, ar), 7.38 (dd, ^3J = 5.0 Hz, J = 3.1 Hz, 1 H, C*H*, ar), 7.10 (t, ^3J = 4.9 Hz, 1 H, C*H*, ar); $^{13}C\{^1H\}$ NMR (125.77 MHz, $CDCl_3$) δ 160.9, 156.2, 140.6, 127.0, 126.3, 125.1, 117.6; ^{15}N NMR (50.69 MHz, $CDCl_3$) δ −95.4; HRMS calcd for $C_8H_6N_2S$: 162.0253, found 162.02548.

2-Butoxypyrimidine (Table 2, entry 4). ^1H NMR (500 MHz, $CDCl_3$) δ 8.43 (d, ^3J = 4.8 Hz, 2 H, C*H*, ar), 6.83 (t, ^3J = 4.8 Hz, 1 H, C*H*, ar), 4.28 (t, ^3J = 6.8 Hz, 2 H, OCH_2), 1.76–1.70 (m, 2 H, CH_2), 1.44 (qui, ^3J = 7.4 Hz, 2 H, CH_2), 0.90 (t, ^3J = 7.5 Hz, 2 H, CH_3); $^{13}C\{^1H\}$ NMR (125.77 MHz, $CDCl_3$) δ 164.35, 158,2, 113.7, 66.4, 29.9, 18.1, 12.8; HRMS calcd for $C_8H_{12}N_2O$: 152.0949, found 152.06218.

3-*p*Tolylthiophene (Table 2, entry 5/Table 3 entry 8). ^1H NMR (500 MHz, $CDCl_3$) δ 7.41 (d, ^3J = 8.0 Hz, 2 H, C*H*, ar), 7.32 (t, J = 2.0 Hz, 1 H, C*H*, ar), 7.29 (s, 1 H, C*H*, ar), 7.29 (t, J = 1.0 Hz, 1 H, C*H*, ar), 7.29 (d, ^3J = 8.0 Hz, 2 H, C*H*, ar), 2.29 (s, 3 H, CH_3); $^{13}C\{^1H\}$ NMR (125.77 MHz, $CDCl_3$) δ 141.3, 135.8, 132.1, 128.5 (2x), 125.3, 125.0, 118.6, 20.1; HRMS calcd for $C_{11}H_{10}S$: 174.0504, found 174.04988.

2-Thiophen-2-ylpyridine (Table 2, entry 6/Table 4, entry 1). ^1H NMR (500 MHz, $CDCl_3$) δ 8.56 (dt, ^3J = 4.5 Hz, J = 1.2 Hz, 1 H, C*H*, ar), 7.68–7.62 (m, 2 H, C*H*, ar), 7.56 (dd, ^3J = 3.8 Hz, J = 1.2 Hz, 1 H, C*H*, ar), 7.38 (dd, ^3J = 5.0 Hz, J = 1.0 Hz, 1 H, C*H*, ar), 7.14–7.09 (m, 2 H, C*H*, ar); $^{13}C\{^1H\}$ NMR (125.77 MHz, $CDCl_3$) δ 151.6, 148.5, 143.8, 135.6, 127.0, 127.5, 123.5, 120.9, 117.8; HRMS calcd for C_9H_7NS: 161.03, found 161.02942.

2-Thiophen-2-ylquinoline (Table 4, entry 2). ^1H NMR (500 MHz, $CDCl_3$) δ 8.11 (d, ^3J = 8.6 Hz, 1 H, C*H*, ar), 8.08 (d, ^3J = 8.5 Hz, 1 H, C*H*, ar), 7.78 (d, ^3J = 8.5 Hz, 1 H, C*H*, ar), 7.75 (dd, ^3J = 8.2 Hz, J = 1.3 Hz, 1 H, C*H*, ar), 7.72 (dd, J = 3.8 Hz, J = 1.2 Hz, 1 H, C*H*, ar), 7.68 (ddd, ^3J = 8.5 Hz, ^3J = 7.0 Hz, J = 1.5 Hz, 1 H, C*H*, ar), 7.47 (ddd, ^3J = 8.0 Hz, ^3J = 6.7 Hz, J = 1.0 Hz, 1 H, C*H*, ar), 7.46 (dd, ^3J = 5.0 Hz, J = 1.0 Hz, 1 H, C*H*, ar), 7.15 (dd, ^3J = 5.0 Hz, J = 3.8 Hz, 1 H, C*H*, ar); $^{13}C\{^1H\}$ NMR (125.77 MHz, $CDCl_3$) δ 151.3, 147.1, 144.4, 135.6, 128.8, 128.3, 127.5, 127.0, 126.4, 126.2, 125.1, 124.8, 116.6; HRMS calcd for $C_{13}H_9NS$: 211.0456, found 211.04476.

4-Methyl-2-thiophen-2-ylquinoline (Table 2, entry 7/Table 4, entry 3). ^1H NMR (500 MHz, $CDCl_3$) δ 8.05 (d, ^3J = 8.2 Hz, 1 H, C*H*, ar), 7.81 (dd, ^3J = 8.2 Hz, J = 1.3 Hz, 1 H, C*H*, ar), 7.63 (dd, ^3J = 3.5 Hz, J = 1.0 Hz, 1 H, C*H*, ar), 7.61 (ddd, ^3J = 8.6 Hz, ^3J = 7.0 Hz, J = 1.6 Hz, 1 H, C*H*, ar), 7.51 (s, 1 H, C*H*, ar), 7.40 (ddd, ^3J = 8.3 Hz, ^3J = 7.0 Hz, J = 1.3 Hz, 1 H, C*H*, ar),7.39 (dd, ^3J = 5.0 Hz, J = 1.3 Hz, 1 H, C*H*, ar), 2.59 (s, 3 H, CH_3); $^{13}C\{^1H\}$ NMR (125.77 MHz, $CDCl_3$) δ 152.4, 148.4, 146.0, 145.1, 130.2, 129.8, 128.7, 128.4, 127.7, 126.2, 126.1, 124.0, 118.6, 19.2; HRMS calcd for $C_{14}H_{11}NS$: 225.0613, found 225.05936.

2-Thiophen-2-ylpyrimidine (Table 2, entry 10/Table 4, entry 6). ^1H NMR (500 MHz, $CDCl_3$) δ 8.62 (d, ^3J = 5.0 Hz, 2 H, C*H*, ar), 7.94 (dd, ^3J = 3.8 Hz, J = 1.3 Hz, 1 H, C*H*, ar), 7.41 (dd, ^3J = 5.0 Hz, J = 1.3 Hz, 1 H, C*H*, ar), 7.08 (dd, ^3J = 5.0 Hz, J = 3.7 Hz, 1 H, C*H*, ar), 7.02 (t, ^3J = 5.0 Hz, 1 H, C*H*, ar); $^{13}C\{^1H\}$ NMR (125.77 MHz, $CDCl_3$) δ 160.6, 156.2, 142.2, 128.9, 128.0, 127.3, 117.5; HRMS calcd for $C_8H_6N_2S$: 162.0253, found 162.02788.

2,4-Dimethoxy-6-thiophen-2-yl-[1,3,5]triazine (Table 4, entry 7). ^1H NMR (500 MHz, $CDCl_3$) δ 8.15 (dd, ^3J = 3.8 Hz, J = 1.3 Hz, 1 H, C*H*, ar), 7.59 (dd, ^3J = 5.0 Hz, J = 1.3 Hz, 1 H, C*H*, ar), 7.16 (dd, ^3J = 5.0 Hz, ^3J = 3.8 Hz, 1 H, C*H*, ar), 4.09 (s, 6 H, OCH_3); $^{13}C\{^1H\}$ NMR (125.77 MHz, $CDCl_3$) δ 171.6, 169.7, 139.7, 131.5, 130.9, 127.3, 54.2; HRMS calcd for $C_9H_9N_3O_2S$: 223.0416, found 223.03932.

2-Furan-3-ylpyridine (Table 5, entry 1). ^1H NMR (500 MHz, $CDCl_3$) δ 8.58 (dq, ^3J = 4.8 Hz, J = 0.9 Hz, 1 H, C*H*, ar), 8.02 (dd, J = 1.5 Hz, J = 0.9 Hz, 1 H, C*H*, ar), 7.65 (dt, ^3J = 7.8 Hz, J = 1.8 Hz, 1 H, C*H*, ar), 7.49 (t, J = 1.8 Hz, 1 H, C*H*, ar), 7.44 (dt, ^3J = 7.9 Hz, J = 1.0 Hz, 1 H, C*H*, ar), 7.12 (ddd, ^3J = 7.6 Hz, J = 4.8 Hz, J = 1.1 Hz, 1 H, C*H*, ar), 6.89 (dd, J = 1.8 Hz, J = 0.8 Hz, 1 H, C*H*, ar); $^{13}C\{^1H\}$ NMR (125.77 MHz, $CDCl_3$) δ 152.2, 150.1, 144.2, 141.6, 136.9, 127.5, 122.1, 120.5, 109.0; ^{15}N NMR (50.69 MHz, $CDCl_3$) δ −76.7; HRMS calcd for C_9H_7NO: 145.0528, found 145.05257. The ^1H NMR spectrum was identical to that in the literature.[63]

2-Furan-3-ylquinoline-3-carbaldehyde (Table 5, entry 2). ^1H NMR (500 MHz, $CDCl_3$) δ 10.41 (s, 1 H, C*H*O), 8.74 (s, 1 H, C*H*, ar), 8.13 (dq, ^3J = 8.5 Hz, J = 0.8 Hz, 1 H, C*H*, ar), 7.95 (d, ^3J = 8.3 Hz, 1 H, C*H*, ar), 7.90–7.89 (m, 1 H, C*H*, ar), 7.83 (ddd, ^3J = 8.5 Hz, ^3J = 6.9 Hz, J = 1.4 Hz, 1 H, C*H*, ar), 7.61 (t, J = 1.7 Hz, 1 H, C*H*, ar), 7.59 (ddd, ^3J = 8.1 Hz, ^3J = 7.1 Hz, J = 1.2 Hz, 1 H, C*H*, ar), 6.95 (q, J = 0.9 Hz, 1 H, C*H*, ar); $^{13}C\{^1H\}$

(63) Ribereau, P.; Queguiner, G. *Can. J. Chem.* **1983**, *61*, 334–342.

NMR (125.77 MHz, $CDCl_3$) δ 190.2, 151.3, 148.9, 142.7, 142.5, 137.5, 131.6, 128.4, 128.3, 126.8, 126.4, 125.1, 123.3, 110.7; ^{15}N NMR (50.69 MHz, $CDCl_3$) δ −71.2; HRMS calcd for $C_{14}H_9NO_2$: 223.0633, found 223.06263.

2-Furan-3-yl-6-methoxypyridine (Table 5, entry 3). ^1H NMR (500 MHz, $CDCl_3$) δ 8.00 (dd, J = 1.6 Hz, J = 0.9 Hz, 1 H, C*H*, ar), 7.53 (dd, ^3J = 8.2 Hz, ^3J = 7.4 Hz, 1 H, C*H*, ar), 7.46 (t, J = 1.7 Hz, 1 H, C*H*, ar), 7.01 (dd, ^3J = 7.4 Hz, J = 0.6 Hz, 1 H, C*H*, ar), 6.85 (dd, J = 1.9 Hz, J = 0.9 Hz, 1 H, C*H*, ar), 7.59 (dd, ^3J = 8.2 Hz, J = 0.6 Hz, 1 H, C*H*, ar), 3.96 (s, 3 H, OCH_3); $^{13}C\{^1H\}$ NMR (125.77 MHz, $CDCl_3$) δ 162.7, 148.2, 142.6, 140.2, 137.9, 126.0, 111.4, 107.7, 107.6, 52.1; ^{15}N NMR (50.69 MHz, $CDCl_3$) δ −120.8; HRMS calcd for $C_{10}H_9NO_2$: 175.0633, found 175.06154.

2-Furan-3-ylpyridin-4-ylamine (Table 5, entry 4). ^1H NMR (500 MHz, $CDCl_3$) δ 8.17 (dd, ^3J = 5.7 Hz 1 H, C*H*, ar), 7.94 (s, 1 H, C*H*, ar), 7.45−7.43 (m, 1 H, C*H*, ar), 6.81−6.78 (m, 1 H, C*H*, ar), 6.67 (d, J = 2.0 Hz, 1 H, C*H*, ar), 6.38 (dd, ^3J = 5.6 Hz, J = 2.1 Hz, 1 H, C*H*, ar), 4.44 (s (br), 1 H, NH_2); $^{13}C\{^1H\}$ NMR (125.77 MHz, $CDCl_3$) δ 152.6, 151.2, 149.0, 142.6, 140.0, 126.2, 107.6, 107.1, 104.8; ^{15}N NMR (50.69 MHz, $CDCl_3$) δ −317.6 (NH_2); HRMS calcd for $C_9H_8N_2O$: 116.00637, found 160.06261.

2-Furan-3-ylpyrimidine (Table 5, entry 5). ^1H NMR (500 MHz, $CDCl_3$) δ 8.69 (d, ^3J = 4.8 Hz, 2 H, C*H*, ar), 8.27−8.26 (m, 1 H, C*H*, ar), 7.50 (t, J = 1.7 Hz, 1 H, C*H*, ar), 7.08 (t, ^3J = 4.9 Hz, 1 H, C*H*, ar), 7.07−7.06 (m, 1 H, C*H*, ar); $^{13}C\{^1H\}$ NMR (125.77 MHz, $CDCl_3$) δ 160.4, 156.1, 143.8, 142.9, 126.0, 117.5, 108.4; ^{15}N NMR (50.69 MHz, $CDCl_3$) δ −95.4; HRMS calcd for $C_8H_6N_2O$: 146.048, found 146.04496.

5-Pyridin-2-ylfuran-2-carbaldehyde (Table 5, entry 6). ^1H NMR (500 MHz, $CDCl_3$) δ 9.72 (s, 1 H, C*H*O), 8.66 (dq, ^3J = 4.7 Hz, J = 0.9 Hz, 1 H, C*H*, ar), 7.92 (dt, ^3J = 7.9 Hz, J = 0.9 Hz, 1 H, C*H*, ar), 7.79 (dt, ^3J = 7.8 Hz, J = 1.8 Hz, 1 H, C*H*, ar), 7.36 (d, J = 3.8 Hz, 1 H, C*H*, ar), 7.29 (ddd, ^3J = 7.6 Hz, J = 4.7 Hz, J = 1.2 Hz, 1 H, C*H*, ar), 7.26 (d, J = 3.8 Hz, 1 H, C*H*, ar); $^{13}C\{^1H\}$ NMR (125.77 MHz, $CDCl_3$) δ 176.7, 157.3, 151.6, 149.0, 146.8, 135.9, 122.8, 121.9, 119.1, 109.7; ^{15}N NMR (50.69 MHz, $CDCl_3$) δ −76.3; HRMS calcd for $C_{10}H_7NO_2$: 173.0477, found 173.04588.

1-(4-Furan-3-ylphenyl)ethanone (Table 5, entry 7). ^1H NMR (500 MHz, $CDCl_3$) δ 7.96 (d, ^3J = 8.2 Hz, 2 H, C*H*, ar), 7.82−7.81 (m, 1 H, C*H*, ar), 7.56 (d, ^3J = 8.2 Hz, 2 H, C*H*, ar), 7.51−7.50 (m, 1 H, C*H*, ar), 6.74−6.73 (m, 1 H, C*H*, ar), 2.60 (s, 3 H, CH_3); $^{13}C\{^1H\}$ NMR (125.77 MHz, $CDCl_3$) δ 196.4, 143.1, 138.6, 136.2, 134.6, 128.0, 124.7, 124.6, 107.6, 25.5; HRMS calcd for $C_{12}H_{10}O_2$: 186.068, found 186.06642. The NMR spectra were identical to those in the literature.[22]

5-Furan-3-yl-2-methylbenzothiazole (Table 5, entry 8). ^1H NMR (500 MHz, $CDCl_3$) δ 8.06 (d, J = 1.6 Hz, 1 H, C*H*, ar), 7.80 (dd, ^3J = 8.2 Hz, J = 0.6 Hz, 1 H, C*H*, ar), 7.80 (dd, J = 1.6 Hz, J = 0.9 Hz, 1 H, C*H*, ar), 7.51 (t, J = 1.7 Hz, 1 H, C*H*, ar), 7.49 (dd, ^3J = 8.3 Hz, J = 1.7 Hz, 1 H, C*H*, ar), 6.77 (dd, J = 1.8 Hz, J = 0.9 Hz, 1 H, C*H*, ar), 2.84 (s, 3 H, CH_3); $^{13}C\{^1H\}$ NMR (125.77 MHz, $CDCl_3$) δ 166.7, 153.1, 142.8, 137.7, 133.1, 129.7, 125.2, 121.9, 120.6, 118.4, 108.0, 19.2; ^{15}N NMR (50.69 MHz, $CDCl_3$) δ −73.9; HRMS calcd for $C_{12}H_9NOS$: 215.0405, found 215.03914.

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Supporting Information Available: Contains the full set of ^1H, ^{13}C and ^{15}N NMR spectra of all compounds synthesized. This material is available free of charge via the Internet at http://pubs.acs.org.

JO8001886

4.7. Nachhaltige Sonogashira-Kreuzkupplungen heterocyclischer Substrate in Wasser/Isopropanol als Reaktionsmedium

Der Inhalt dieses Kapitels wurde bereits veröffentlicht:

Christoph A. Fleckenstein, Herbert Plenio, *"Aqueous/Organic Cross Coupling: Sustainable Protocol for Sonogashira Reactions of Heterocycles"*, *Green Chem*. **2008**, *10*, 563-570.

Dieses Kapitel beschreibt die Entwicklung eines nachhaltigen Verfahrens für Sonogashira-Kreuzkupplungsreaktionen in wässrigem Reaktionsmedium mit Pd-*cataCXium® FSulf* als Katalysator.

Vorteile des neuen Verfahrens sind:

- quantitative Kupplung heterocyclischer und nichtheterocyclischer Brom- oder Chloraromaten mit diversen terminalen Alkinen
- Wasser/Isopropanol (1:1) als preiswertes, nichttoxisches und biologisch abbaubares Reaktionsmedium
- Minimierung von Abfällen und erhöhte Reaktionssicherheit durch kupferfreies Syntheseprotokoll
- Einsatz von Kaliumcarbonat als preiswerte, nichttoxische und gefahrlose Base
- angenehme Reaktionsbedingungen (90 °C)
- bei Synthesen in technischem Maßstab: vorteilhafte Separation des Kupplungsprodukts in der bei Raumtemperatur nicht wassermischbaren organischen Phase von anorganischen Reagenzien und Nebenprodukten ohne Zusatz weiterer organischer Lösemittel

Anhand von dreiundzwanzig verschiedenen Sonogashira-Kupplungsreaktionen werden Robustheit sowie Grenzen des Verfahrens aufgezeigt. Die quantitative Kupplung der Substrate gelingt mit 1 mol% Katalysatorbeladung. Das Syntheseprotokoll toleriert problemlos eine Vielzahl diverser Heterocyclen (z.B. Pyridine, Pyrimidine, Furane, Thiophene…), ungeschützte Aminofunktionalitäten, sterisch gehinderte Substrate, aliphatische oder aromatische Alkine ebenso wie Ethinylferrocen.

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Aqueous/organic cross coupling: Sustainable protocol for Sonogashira reactions of heterocycles†

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The water soluble Pd complex of dicyclohexyl(2-sulfo-9-(3-(4-sulfophenyl)propyl)-9*H*-fluoren-9-yl)phosphine was used for an efficient copper free and sustainable reaction protocol for Sonogashira cross couplings. Using a water/*i*propanol mixture as the solvent and K_2CO_3 as base, numerous heterocyclic and aryl bromides and chlorides were reacted with various acetylenes in near quantitative yield at 1 mol% catalyst loading and 90 °C.

Introduction

Compounds bearing carbon–carbon triple bonds are ubiquitous in pharmaceuticals and fine chemicals;[1,2] examples are tazarotene,[3] terbinafin[4,5] or the oncology candidate CP-724,714.[6]

The Sonogashira reaction is a powerful tool to effect C(sp)–C(sp^2)- and C(sp)–C(sp^3) coupling reactions.[1,7–17] However, typical solvents utilized in such reactions, like DMF/DMAc,[8,12,18] DMSO,[19,20] toluene,[14,21] dioxane[9,22] or amine-bases[17] are less favourable from an ecological and economical point of view[23–27] than water.[28] Furthermore, the use of CuI, which is often used as the co-catalyst, can be problematic in large scale reactions due to the formation of insoluble copper-acetylides.[29]

Considering these limitations, it was our intention to develop a Sonogashira protocol for the synthesis of heterocyclic compounds which is more sustainable, safe and useful. This approach is motivated by the fact that the vast majority of biologically active compounds and APIs (active pharmaceutical ingredients) contains heterocyclic structures—often combined with problematic functional groups like free amine moieties.[30–37] Notable, in this respect is recent work from Beller *et al.* who reported on the Sonogashira coupling of various heterocyclic substrates.[38] With Beller the use of TMEDA (tetramethylethylenediamine) as solvent and CuI as the co-catalyst were the key to the efficient transformation of some *N*- and *S*-heterocyclic substrates.

While efforts have been made in designing highly active catalytic systems for Pd cross coupling,[39] the catalyst loading is not the determining factor making a process more benign.[40,41] In (Sonogashira) cross coupling reactions, solvents as well as various additives have by far the largest economical and environmental impact. Hence, it follows that critical organic solvents and additives should be avoided.[42] Water appears to be an obvious alternative,[23,24] but for organic transformations of lipophilic substrates the poor solubility of some organic reactants in water in the absence of other solvents creates problems. Due to several favourable properties, *i*propanol was chosen as the co-solvent: besides decreasing the polarity of the reaction medium and consequently increasing the solubility of organic substrates, it is inexpensive, safe and easily biodegradable *via* the acetone pathway and thus a particularly favourable organic co-solvent.[23,25,42]

For our work, we have tested a broad range of heterocyclic substrates with a view to a sustainable protocol, while on the other hand preserving high catalytic activities.

Results and discussion

We recently reported the synthesis of fluorenyldialkylphosphines[43] whose Pd-complexes are excellent catalysts for various cross coupling reactions.[32,44] The disulfonated derivative **1**·3H$^+$ (Fig. 1) forms highly water soluble Pd-complexes. In combination with aqueous reaction media these complexes showed unprecedented catalytic activity in Suzuki cross coupling of *N*- and *S*- heterocyclic substrates, thus facilitating the synthesis of important heterocyclic building blocks.[31,45] We found out then, that the use of water as a (co-)solvent is essential for good catalytic activity, as hydrogen bonding with the nitrogen donor moieties appears to prevent inhibition of the catalyst.

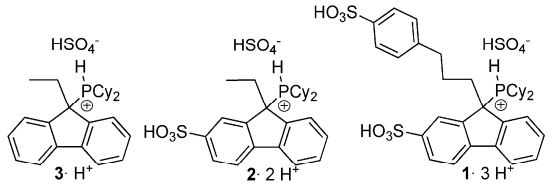

Fig. 1 Fluorenyldicyclohexylphosphine and mono- and disulfonated relative (H_2SO_4 adducts).

In order to extend the scope of Pd complexes with phosphine **1** to other cross coupling reactions, we tested those complexes in Sonogashira cross coupling reactions of heteroaryl chlorides and bromides in a benign aqueous solvent mixture of water/*i*propanol (1 : 1) in combination with unproblematic K_2CO_3

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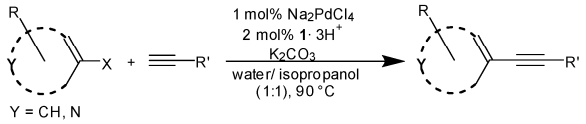
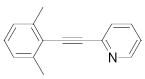
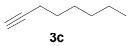
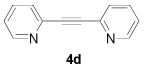
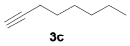
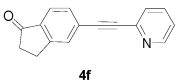
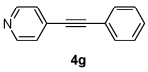
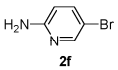
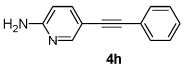
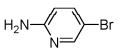
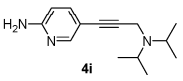
† Electronic supplementary information (ESI) available: Supporting information for this article contains the NMR spectra of all Sonogashira coupling products as well as cyclic voltammograms of the synthesized ferrocenyl derivatives. See DOI: 10.1039/b800154e

Table 1 Sonogashira reactions involving *N*-heterocyclic or *N*-containing substrates[a]



Entry	Aryl halide	Acetylene	Product	*t*/h	Conversion[b]	Yield[c]
1	 **2a**	 **3a**	 **4a**	3	≥99%	94%
2	 **2b**	 **3b**	 **4b**	4 10 10 10 20	≥99% 90%[d] 72%[e] 0%[f] 0%[g]	91%
3	 **2b**	 **3c**	 **4c**	10	≥99%	93%
4	 **2b**	 **3a**	 **4d**	10	≥99%	89%
5	 **2c**	 **3c**	 **4e**	10	≥99%	94%
6	 **2d**	 **3a**	 **4f**	8	≥99%	91%
7	 **2e**	 **3b**	 **4g**	5	≥99%	94%
8	 **2f**	 **3b**	 **4h**	10	89%	85%
9	 **2f**	 **3d**	 **4i**	10	96%	91%

[a] 1.5 mmol aryl chloride, 1.7 mmol acetylene, 2.0 mmol K_2CO_3, 6 mL water/*i*propanol (1 : 1), catalyst 1 mol% (1 mL stock solution : Na_2PdCl_4/ligand (1 : 2)), 90 °C. [b] Determined *via* gas chromatography (heptadecane, internal standard). [c] Average of two runs, column chromatography (silica (15 × 3 cm)). [d] 0.5 mol% Pd-catalyst. [e] 0.1 mol% Pd-catalyst. [f] No Pd-catalyst. [g] 2 mol% Na_2PdCl_4, no ligand.

as base. The catalyst is formed *in situ* from Na_2PdCl_4, and two equivalents of the triply protonated ligand **1**·3H$^+$ in the presence of five equivalents of base.

In a preliminary test the activity of the catalyst was studied in the reaction of 2-chloropyridine with phenylacetylene (Table 1, entry 2). The respective Sonogashira coupling affords the desired coupling product in quantitative yield (4 h, 100 °C, 1 mol% catalyst). Applying 0.1 mol% catalyst 72% conversion is found after 10 h. Tests using 2 mol% Pd salt in absence of phosphine **1** or in complete absence of catalyst gave no conversion in the same reaction.

Interestingly, the Sonogashira cross coupling reactions reported here proceed smoothly without the use of a copper(I)salt as co-catalyst.[46] Others performing this kind of coupling reaction under copper free conditions are either restricted to aryliodides and non-deactivated arylbromides,[47–52] or require severe reaction conditions, like high reaction temperatures,[18,53] microwave activation,[54] or high Pd-catalyst concentrations.[10,37,55,56]

The cross coupling of additional *N*-heteroarylchlorides and other nitrogen-containing substrates with aryl acetylenes in Sonogashira reactions is found in Table 1. The generality of our reaction protocol was demonstrated by reacting a sterically

demanding, deactivated arylhalide with a *N*-heterocyclic acetylene. Utilizing 1 mol% of the Pd-catalyst 2,6-dimethylbromobenzene (**2a**) was quantitatively coupled with 2-pyridylacetylene (**3a**) at 90 °C in 3 h (Table 1, entry 1) in water/*i*propanol (1 : 1) as solvent.

2-Chlorpyridine and 2-chloropyrimidine were successfully coupled with phenyl-, octyl- or 2-pyridylacetylene (Table 1, entries 3–5). 5-Bromo-2-amino-pyridine with a free amino group is a challenging substrate for Pd catalyzed cross coupling reactions. Applying the given conditions, 5-bromo-2-amino-pyridine can be directly coupled with phenylacetylene in near quantitative yield without the need for *N*-protection (Table 1, entry 8).

Next, Sonogashira reactions of *S*- and *O*-heterocyclic substrates were investigated (Table 2). Electron rich and thus deactivated 2-bromothiophene and 3-bromothiophene were coupled in excellent yields with both aliphatic acetylenes (Table 2, entries 1, 8) and arylacetylenes (Table 2, entries 2, 13). The efficient coupling of sulfur containing substrates with nitrogen heterocycles under the same conditions is demonstrated (Table 2, entries 3, 4).

Interesting is the effective coupling of the labile 3-bromofurane with acetylenes. Similar structures have received interest due to their biological activity, but with the exception of the recent Beller publication[38] 3-bromofurane was rarely used in Sonogashira reactions and known to cause problems resulting in poor product yields.[57] With phenylacetylene as the coupling partner, the desired product was obtained in quantitative yield (Table 2, entry 6). Substituted ferrocenes receive interest in medicinal and life science chemistry because of their biological activity in cancer-,[58–63] malaria-[58,64–66] and HIV-treatment[67,68] or as auxiliary in DNA detection.[69–71] To facilitate this chemistry, we investigated some coupling reactions of ferrocenylacetylene with heterocyclic aryl halides. 3-Ferrocenylethynyl-thiophene and 3-ferrocenylethynyl-furan were obtained in yields of around 95% and excellent purity (Table 2, entries 5, 7).

The coupling of the unprotected and deactivated 2-bromoaniline with 2-ethynylthiophene selectively yielded the Sonogashira coupling product (Table 2, entry 12). In the same manner, unprotected 5-bromo-2-amino-pyridine is coupled with 2-ethinylthiophene in 93% yield (table 2, entry 14). When propargylic alcohols were used as coupling partners (table 2, entry 11), no coupling product was observed. This was not entirely unexpected as we had learnt earlier, that propargylic alcohols can be reacted in Sonogashira reactions only under strict exclusion of water.[17]

Due to the significant amount of salts, the reaction mixture consisting of water, *i*propanol and the reactants form two phases. Hence, in a larger scale synthesis of heterocycles using the Sonogashira coupling, we were able to simply separate the product containing the organic layer from the water solution containing the salts without adding additional non-polar solvent such as ether. Therefore, the whole process can be run as a truly green process utilizing exclusively environmentally neutral water and sustainable, biodegradable *i*propanol as solvents.

Summary

We have developed a sustainable copper free protocol for Sonogashira cross coupling reactions utilizing a benign and easily biodegradable mixture of water and *i*propanol as the solvent. In the presence of 1 mol% of the *in situ* formed Pd/**1** complex, deactivated and sterically hindered arylbromides as well as various *N*-, *S*- or *O*- heterocyclic arylchlorides and bromides are effectively reacted with a variety of hetero and non-hetero acetylenes, including ferrocenylacetylene.

Experimental

All chemicals were purchased as reagent grade from commercial suppliers and used without further purification, unless otherwise noted. Used solvents (water, *i*propanol (technical grade)) were deaerated *via* freeze and thaw technique. Ligand **1**·3H$^+$ is commercially available under the trade name cataCXium F from Degussa GmbH. All experiments were carried out under an argon atmosphere, unless otherwise noted. Proton (^{1}H NMR), carbon (^{13}C NMR) and nitrogen (^{15}N NMR) nuclear magnetic resonance spectra were recorded on a Bruker DRX 500 at 500 MHz, 125.75 MHz, 202.46 MHz and 50.69 MHz, respectively at 293 K. The chemical shifts are given in parts per million (ppm) on the delta scale (δ) and are referenced to tetramethylsilane (^{1}H and ^{13}C NMR: $\delta = 0$ ppm), nitromethane (^{15}N NMR: $\delta = 0$ ppm). Abbreviations for NMR data: s = singlet; d = doublet; t = triplet; q = quartet; qi = quintet; dd = doublet of doublets; dt = doublet of triplets; dq = doublet of quartets; tt = triplet of triplets; m = multiplet. Mass spectra were recorded on a Finnigan MAT 95 magnetic sector spectrometer. Thin layer chromatography (TLC) was performed using Fluka silica gel 60 F 254 (0.2 mm) on Al-plates. Silica gel columns for chromatography were prepared with E. Merck silica gel 60 (0.063–0.20 mesh ASTM). GC experiments were run on a Clarus 500 GC with autosampler and FID detector. Column: Varian CP-Sil 8 CB (l = 15 m, d_i = 0.25 mm, d_F = 1.0 μm), N_2 (flow: 17 cm s^{-1}; split 1 : 50); Injector-temperature: 270 °C, detector temperature: 350 °C. Temperature program: isotherm 150 °C for 5 min, heating to 300 °C with 25 °C min^{-1}, isotherm for 15 min. Cyclic voltammetry: EG & G 263A-2 potentiostat. Cyclic voltammograms were recorded in dry CH_2Cl_2 under an argon atmosphere at ambient temperature. A three-electrode configuration was employed. The working electrode was a Pt disk (diameter 1 mm) sealed in soft glass with a Pt wire as the counter electrode. The pseudo reference electrode was an Ag wire. Potentials were calibrated internally against the formal potential of octamethylferrocene (−0.010 mV (CH_2Cl_2) *vs.* Ag/AgCl). NBu_4PF_6 (0.1 mol L^{-1}) was used as supporting electrolyte.

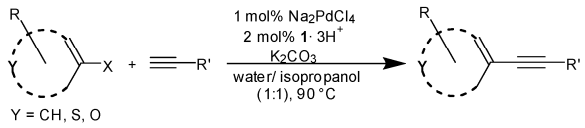
Preparation of the catalyst stock solution

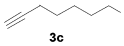
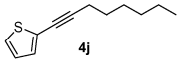
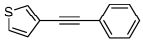
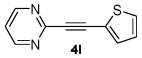
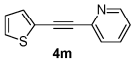
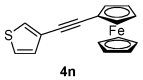
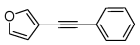
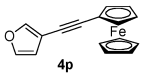
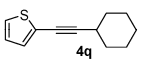
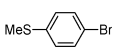
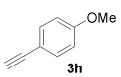
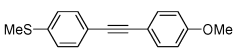
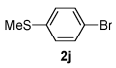
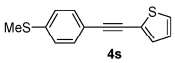
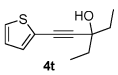
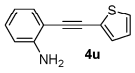
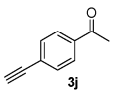
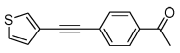
Na_2PdCl_4 (14.7 mg, 0.05 mmol), **1**·3H$^+$ (80 mg, 0.1 mmol) and K_2CO_3 (56 mg, 0.4 mmol) were placed in a Schlenk tube under argon. Degassed water (5.0 mL) was added and the mixture was stirred at 55 °C for 3 h until the clear solution turned nearly colourless (very slightly yellow). This stock solution had a Pd-concentration of 0.01 mol L^{-1}.

Typical screening procedure of cross coupling reactions

K_2CO_3 (2 mmol) was placed in a 25 mL Schlenk tube under an argon atmosphere. Degassed water (1.5 mL) and degassed

Table 2 Sonogashira reactions involving *S*/*O*-heterocyclic or *S*/*O*-containing substrates[a]



Entry	Aryl halide	Acetylene	Product	*t*/h	Conversion[b]	Yield[c]
1	 **2g**	 **3c**	 **4j**	10	≥99%	91%
2	 **2h**	 **3b**	 **4k**	10	≥99%	94%
3	 **2c**	 **3e**	 **4l**	10	≥99%	90%
4	 **2g**	 **3a**	 **4m**	10	≥99%	92%
5	 **2h**	 **3f**	 **4n**	10	≥99%	95%
6	 **2i**	 **3b**	 **4o**	10	≥99%	91%
7	 **2i**	 **3f**	 **4p**	10	≥99%	94%
8	 **2g**	 **3g**	 **4q**	10	98%	91%
9	 **2j**	 **3h**	 **4r**	5	≥99%	95%
10	 **2j**	 **3e**	 **4s**	5	≥99%	95%
11	 **2g**	 **3i**	 **4t**	10	<5%	0
12	 **2k**	 **3e**	 **4u**	5	≥99%	94%
13	 **2h**	 **3j**	 **4v**	5	≥99%	96%
14	**2f**	**3e**	**4w**	5	98%	93%

[a] 1.5 mmol aryl chloride, 1.7 mmol acetylene, 2.0 mmol K_2CO_3, 6 mL water/*i*propanol (1 : 1), catalyst 1 mol% (1 mL stock solution : Na_2PdCl_4/ligand (1 : 2)), 90 °C. [b] Determined *via* gas chromatography (heptadecane internal standard). [c] Average of two runs, column chromatography (silica (15 × 3cm)).

*i*propanol (3 mL) were added as well as the respective aryl halide (1.5 mmol) and acetylene (1.7 mmol). After addition of 1.5 mL catalyst stock solution (1.5 mL = 1 mol% Pd) the reaction mixture was stirred at 90 °C for the given time. After cooling to room temperature the reaction mixture was diluted with ether (10 mL), washed with water (10 mL), the organic phase dried over $MgSO_4$, filtered and concentrated *in vacuo*. The product was isolated by column chromatography (silica, cyclohexane : EtOAc : NEt_3 = 9 : 1 : 1). Alternatively the yield was determined *via* gas chromatography with heptadecane as an internal standard.

Typical "g-scale" procedure of cross coupling reactions

K_2CO_3 (2.76 g, 20 mmol) was placed in a 50 mL Schlenk flask under an argon atmosphere. Degassed water (7.5 mL) and degassed *i*propanol (15 mL) were added, as well as 2-chloropyridine (1.14 g, 939 μL, 10 mmol) and acetylene (1.22 g, 1.32 mL, 12 mmol). After addition of 7.5 mL of the aqueous catalyst stock solution (7.5 mL = 1 mol% Pd-loading) the reaction mixture was stirred at 90 °C for 7 h. After cooling to room temperature, the reaction mixture was transferred into a separation funnel. The upper (organic) layer was isolated, dried over $MgSO_4$ for 10 min, filtered and concentrated *in vacuo*. The product was purified by column chromatography (silica, cyclohexane : EtOAc : NEt_3 = 9 : 1 : 1). Yield: 1.63 g (91%).

2-(2,6-Dimethyl-phenylethynyl)-pyridine (4a)

The crude product was purified *via* column chromatography on silica (cyclohexane : EtOAc : NEt_3 = 9 : 1 : 1). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.64 (ddd, ^5J = 1.0 Hz, ^4J = 1.5 Hz, ^3J = 4.5 Hz, 1 H, C*H*, ar), 7.66 (dt, ^4J = 1.8 Hz, ^3J = 7.3 Hz, 1 H, C*H*, ar), 7.52 (td, ^4J = 1.5 Hz, ^3J = 7.5 Hz, 1 H, C*H*, ar), 7.21 (ddd, ^4J = 1.5 Hz, ^3J = 7.5 Hz, ^3J = 5.0 Hz, 1 H, C*H*, ar), 7.15 (t, ^3J = 8.0 Hz, 1 H, C*H*, ar), 7.07 (d, ^3J = 7.5 Hz, 2 H, C*H*, ar), 2.55 (s, 6 H, CH_3); ^{13}C{^{1}H} NMR (125.77 MHz, $CDCl_3$) δ = 149.1, 142.9, 139.9, 135.0, 127.5, 126.2, 125,7, 121,5 121.0, 96.0, 86.0, 20.1; HRMS calcd. for $C_{15}H_{13}N$: 207.1048, found 207.10290.

2-Phenylethynyl-pyridine (4b)

The crude product was purified *via* column chromatography on silica (cyclohexane : EtOAc : NEt_3 = 9 : 1 : 1). ^{1}H- and ^{13}C NMR-spectra are consistent with those in the literature.[72]

2-Oct-1-ynyl-pyridine (4c)

The crude product was purified *via* column chromatography on silica (cyclohexane : EtOAc : NEt_3 = 9 : 1 : 1). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.64 (ddd, ^5J = 1.0 Hz, ^4J = 1.5 Hz, ^3J = 5.0 Hz, 1 H, C*H*, ar), 7.60 (dt, ^4J = 2.0 Hz, ^3J = 8.5 Hz, 1 H, C*H*, ar), 7.36 (td, ^4J = 1.0 Hz, ^3J = 8.0 Hz, 1 H, C*H*, ar), 7.17 (ddd, ^4J = 1.0 Hz, ^3J = 7.5 Hz, ^3J = 5.0 Hz, 1 H, C*H*, ar), 2.43 (t, ^3J = 7.0 Hz, 2 H, C–CH_2), 1.63 (qui, ^3J = 7.0 Hz, 2 H, CH_2), 1.49–1.42 (m, 2 H, CH_2), 1.37–1.27 (m, 4 H, CH_2), 0.90 (t, ^3J = 7.0 Hz, 3 H, CH_3); ^{13}C{^{1}H} NMR (125.77 MHz, $CDCl_3$) δ = 149.8, 144.1, 136.0, 126.8, 122.2, 91.2, 80.4, 31.4, 28.7, 28.4, 22.5, 19.4, 14.1; HRMS calcd. for $C_{13}H_{17}N$: 187.1361, found 187.13295. ^{1}H- and ^{13}C NMR-spectra are literature consistent.[73]

1,2-Di-(2,2′-pyridyl)-ethyne (4d)

The crude product was purified *via* column chromatography on silica (cyclohexane : EtOAc : NEt_3 = 9 : 1 : 1). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.54 (ddd, ^5J = 0.9 Hz, ^4J = 1.8 Hz, ^3J = 4.8 Hz, 2 H, C*H*, ar), 7.63 (dt, ^4J = 1.8 Hz, ^3J = 7.8 Hz, 2 H, C*H*, ar), 7.55 (td, ^4J = 1.5 Hz, ^3J = 7.5 Hz, 2 H, C*H*, ar), 7.21 (ddd, ^4J = 1.2 Hz, ^3J = 5.0 Hz, ^3J = 8.3 Hz, 2 H, C*H*, ar; ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ = 149.2, 141.7, 135.2, 126.8, 122.4, 86.9; HRMS calcd. for $C_{12}H_8N_2$: 180.0688, found 180.06814.

2-Oct-1-ynyl-pyrimidine (4e)

The crude product was purified *via* column chromatography on silica (cyclohexane : EtOAc : NEt_3 = 9 : 2 : 1). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.68 (d, ^3J = 5.0 Hz, 2 H, C*H*, ar), 7.19 (dt, ^3J = 5.0 Hz, 1 H, C*H*, ar), 2.47 (t, ^3J = 7.5 Hz, 2 H, C–CH_2), 1.66 (qui, ^3J = 7.0 Hz, 2 H, CH_2), 1.51–1.42 (m, 2 H, CH_2), 1.36–1.25 (m, 4 H, CH_2), 0.89 (t, ^3J = 6.5 Hz, 3 H, CH_3); ^{13}C{^{1}H} NMR (125.77 MHz, $CDCl_3$) δ = 157.6, 153.8, 119.7, 91.2, 80.3, 31.7, 29.0, 28.4, 22.9, 19.6, 14.4; HRMS calcd. for $C_{12}H_{16}N_2$: 188.1314, found 188.13016.

5-Pyridin-2-ylethynyl-indan-1-one (4f)

The crude product was purified *via* column chromatography on silica (cyclohexane : EtOAc : NEt_3 = 9 : 2 : 1). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.57–8.53 (m, 1 H, CH_{ar}), 7.65–7.57 (m, 3 H, CH_{ar}), 7.49–7.43 (m, 2 H, CH_{ar}), 7.21–7.16 (m, 1 H, CH_{ar}), 3.04 (t, ^3J = 5.1 Hz, 2 H, CH_2), 2.63–2.58 (m, 2 H, CH_2); ^{13}C{^{1}H} NMR (125.77 MHz, $CDCl_3$) δ = 204.9, 153.8, 149.2, 141.8, 136.0, 135.2, 130.1, 129.1, 127.4, 126.4, 122.6, 122.2, 90.5, 87.3, 35.3, 24.6; ^{15}N NMR (50.69 MHz,$CDCl_3$) δ = −64.6; HRMS calcd. for $C_{16}H_{11}NO$: 233.0841, found 233.08329.

4-Phenylethynyl-pyridine (4g)

The crude product was purified *via* column chromatography on silica (cyclohexane : EtOAc : NEt_3 = 9 : 2 : 1). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.60 (dd, ^3J = 4.5 Hz, J = 1.6 Hz, 2 H, C*H*, ar), 7.56–7.54 (m, 2 H, C*H*, ar), 7.39–7.36 (m, 5 H, C*H*, ar); ^{13}C{^{1}H} NMR (125.77 MHz, $CDCl_3$) δ = 149.9, 132.0, 131.6, 129.3, 128.6, 125.7, 122.3, 94.1, 86.8; ^{15}N NMR (50.69 MHz,$CDCl_3$) δ = −68.9; HRMS calcd. for $C_{13}H_9N$: 179.0735, found 179.07323.

5-Phenylethynyl-pyridin-2-ylamine (4h)

The crude product was purified *via* column chromatography on silica (cyclohexane : EtOAc : NEt_3 = 5 : 5 : 1). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.28 (dd, J = 2.2 Hz, J = 0.7 Hz, 1 H, CH_{ar}), 7.56 (dd, ^3J = 8.5 Hz, J = 2.2 Hz, 1 H, CH_{ar}), 7.51–7.48 (m, 2 H, CH_{ar}), 7.36–7.29 (m, 3 H, CH_{ar}), 6.46 (dd, ^3J = 8.5 Hz, J = 0.7 Hz, 1 H, CH_{ar}), 4.66 (s(br), 2 H, NH_2); ^{13}C{^{1}H} NMR (125.77 MHz, $CDCl_3$) δ = 156.5, 150.5, 139.4, 130.4, 127.3, 127.0, 122.4, 108.9, 106.9, 88.8, 86.0; ^{15}N-NMR (50.7 MHz, $CDCl_3$) δ = −114.7 (Pyr-*N*), (*N*H_2): signal not observed; HRMS calcd. for $C_{13}H_{10}N_2$: 194.0844, found 194.08527.

5-(3-Diisopropylamino-prop-1-ynyl)-pyridin-2-ylamine (4i)

The crude product was purified *via* column chromatography on silica (cyclohexane : EtOAc : NEt_3 = 5 : 5 : 1). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.12 (d, J = 2.2 Hz, 1 H, CH_{ar}), 7.41 (dd, ^3J = 8.5 Hz, J = 2.2 Hz, 1 H, CH_{ar}), 6.40 (dd, ^3J = 8.5 Hz, J = 0.7 Hz, 1 H, CH_{ar}), 4.71 (s(br), 2 H, NH_2), 3.61 (s, 2 H, CH_2), 3.42 (sept, ^3J = 6.7 Hz, 2 H, CH_{ipr}), 1.13 (d, ^3J = 6.7 Hz, 12 H, CH_3); ^{13}C{^{1}H} NMR (125.77 MHz, $CDCl_3$) δ = 157.7, 151.5, 140.7, 110.7, 108.2, 89.7, 81.1, 48.9, 35.3, 21.0; ^{15}N-NMR (50.7 MHz, $CDCl_3$) δ = −114.6 (Pyr-N), −309.0 (NH$_2$), −323.9 (N^iPr$_2$); HRMS calcd. for $C_{14}H_{21}N_3$: 231.1736, found 231.17283.

2-Oct-1-ynyl-thiophene (4j)

The crude product was purified *via* column chromatography on silica (cyclohexane : EtOAc = 9 : 1). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.15 (dd, ^3J = 5.0 Hz, J = 1.0 Hz, 1 H, C$H_{thiophene}$), 7.10 (dd, ^3J = 3.6 Hz, J = 1.0 Hz, 1 H, C$H_{thiophene}$), 6.92 (dd, ^3J = 5.0 Hz, J = 3.6 Hz, 1 H, C$H_{thiophene}$), 2.41 (t, ^3J = 7.2 Hz, 2 H, CCCH_2), 1.62–1.56 (m, 2 H, CH_2), 1.47–1.39 (m, 2 H, CH_2), 1.35–1.24 (m, 4 H, CH_2), 0.90 (t, ^3J = 7.0 Hz, 3 H, CH_3); ^{13}C{^{1}H} NMR (125.77 MHz, $CDCl_3$) δ = 130.9, 126.7, 125.8, 124.3, 94.6, 73.7, 31.4, 28.6, 22.6, 22.5, 19.7, 14.0; HRMS calcd. for $C_{12}H_{16}S$: 192.0973, found 192.09713. ^{1}H- and ^{13}C NMR-spectra are literature consistent.[74]

3-Phenylethynyl-thiophene (4k)

The crude product was purified *via* column chromatography on silica (cyclohexane : EtOAc = 9 : 1). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.52–7.49 (m, 3 H, C$H_{thiophene}$ + CH_{ar}), 7.34–7.29 (m, 3 H, CH_{ar}), 7.27 (dd, ^3J = 5.0 Hz, J = 3.0 Hz, 1 H, C$H_{thiophene}$), 7.19 (dd, ^3J = 5.0 Hz, J = 1.2 Hz, 1 H, C$H_{thiophene}$); ^{13}C{^{1}H} NMR (125.77 MHz, $CDCl_3$) δ = 131.5, 129.9, 128.6, 128.3, 128.2, 125.3, 123.2, 122.3, 88.9, 84.5; HRMS calcd. for $C_{12}H_8S$: 184.0347, found 184.03444. ^{1}H- and ^{13}C NMR-spectra are literature consistent.[52]

2-Thiophen-2-ylethynyl-pyrimidine (4l)

The crude product was purified *via* column chromatography on silica (cyclohexane : EtOAc : NEt_3 = 9 : 2 : 1). H NMR (500 MHz, $CDCl_3$) δ = 8.75 (d, ^3J = 5.0 Hz, 2 H, CH_{ar}), 7.50 (dd, ^3J = 3.7 Hz, J = 1.1 Hz, 1 H, C$H_{thiophene}$), 7.41 (dd, ^3J = 5.1 Hz, J = 1.1 Hz, 1 H, C$H_{thiophene}$), 7.23 (t, ^3J = 5.0 Hz, 1 H, CH_{ar}), 7.05 (dd, ^3J = 5.1 Hz, ^3J = 3.7 Hz, 1 H, C$H_{thiophene}$); ^{13}C{^{1}H} NMR (125.77 MHz, $CDCl_3$) δ = 157.4, 153.3, 134.9, 129.7, 127.4, 121.3, 119.6, 91.9, 81.8; ^{15}N-NMR (50.7 MHz, $CDCl_3$) δ = −85.2; HRMS calcd. for $C_{10}H_6N_2S$: 186.0253, found 186.02351.

2-Thiophen-2-ylethynyl-pyridine (4m)

The crude product was purified *via* column chromatography on silica (cyclohexane : EtOAc : NEt_3 = 9 : 1 : 1). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.62 (ddd, ^3J = 5.0 Hz, J = 1.8 Hz, J = 1.0 Hz, 1 H, CH_{pyr}), 7.67 (dt, ^3J = 7.8 Hz, J = 1.8 Hz, 1 H, CH_{pyr}), 7.50 (dt, ^3J = 7.8 Hz, J = 1.0 Hz, 1 H, CH_{pyr}), 7.38 (dd, ^3J = 3.7 Hz, J = 1.2 Hz, 1 H, C$H_{thiophene}$), 7.34 (dd, ^3J = 5.3 Hz, J = 1.2 Hz, 1 H, C$H_{thiophene}$), 7.23 (ddd, ^3J = 7.7 Hz, ^3J = 5.0 Hz, J = 1.2 Hz, 1 H, CH_{pyr}), 7.03 (dd, ^3J = 5.2 Hz, ^3J = 3.7 Hz, 1 H, C$H_{thiophene}$); ^{13}C{^{1}H} NMR (125.77 MHz, $CDCl_3$) δ = 150.2, 143.3, 136.2, 133.4, 128.4, 127.3, 127.0, 122.9, 122.3, 92.4, 82.8; ^{15}N-NMR (50.7 MHz, $CDCl_3$) δ = −67.5; HRMS calcd. for $C_{11}H_7NS$: 185.0300, found 185.02890. The ^{1}H NMR-spectrum is literature consistent.[75]

3-Ferrocenylethynyl-thiophene (4n)

The crude product was purified *via* column chromatography on silica (*n*heptane). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.44 (dd, ^3J = 3.0 Hz, J = 1.1 Hz, 1 H, C$H_{thiophene}$), 7.27 (dd, ^3J = 5.0 Hz, ^3J = 3.0 Hz, 1 H, C$H_{thiophene}$), 7.15 (dd, ^3J = 5.0 Hz, J = 1.1 Hz, 1 H, C$H_{thiophene}$), 4.48 (t, ^3J = 1.9 Hz, 2 H, CH_{Fc}), 4.24 (s, 5 H, CH_{Fc}), 4.22 (t, ^3J = 1.9 Hz, 2 H, CH_{Fc}); ^{13}C{^{1}H} NMR (125.77 MHz, $CDCl_3$) δ = 129.9, 127.7, 125.1, 122.9, 87.7, 80.7, 71.3, 70.0, 68.8, 65.2; CV: ($E_{1/2}$ = 0.550 V; ΔE = 92 mV); HRMS calcd. for $C_{16}H_{12}SFe$: 292.0009, found 292.00108.

3-Phenylethynyl-furan (4o)

The crude product was purified *via* column chromatography on silica (cyclohexane : EtOAc = 200 : 1). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.68 (dd, J = 1.6 Hz, J = 0.9 Hz, 1 H, CH_{furyl}), 7.50–7.47 (m, 2 H, CH_{ar}), 7.39 (dd, J = 1.9 Hz, J = 1.6 Hz, 1 H, CH_{furyl}), 7.33–7.30 (m, 3 H, CH_{ar}), 6.52 (dd, J = 1.9 Hz, J = 0.6 Hz, 1 H, CH_{furyl}); ^{13}C{^{1}H} NMR (125.77 MHz, $CDCl_3$) δ = 145.6, 142.9, 132.5, 131.4, 128.4, 128.2, 123.2, 112.6, 91.0, 80.5; HRMS calcd. for $C_{12}H_8O$: 168.0575, found 168.06009.

3-Ferrocenylethynyl-furan (4p)

The crude product was purified *via* column chromatography on silica (*n*heptane). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.65–7.63 (m, 1H, CH_{furyl}), 7.38–7.36 (m, 1H, CH_{furyl}), 7.48 (d, J = 1.3 Hz, 1 H, CH_{furyl}), 4.47 (t, ^3J = 1.8 Hz, 2 H, CH_{Fc}), 4.23 (s, 5 H, CH_{Fc}), 4.22 (t, ^3J = 1.8 Hz, 2 H, CH_{Fc}); ^{13}C{^{1}H} NMR (125.77 MHz, $CDCl_3$) δ = 144.07, 141.67, 111.62, 107.13, 88.63, 75.46, 70.27, 68.96, 67.72, 64.30; CV: ($E_{1/2}$ = 0.546 V; ΔE = 82 mV); HRMS calcd. for $C_{16}H_{12}OFe$: 276.0237, found 276.0223.

2-Cyclohexylethynyl-thiophene (4q)

The crude product was purified *via* column chromatography on silica (*n*pentane : EtOAc = 200 : 1). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.15 (dd, ^3J = 5.2 Hz, J = 1.2 Hz, 1 H, C$H_{thiophene}$), 7.10 (dd, ^3J = 3.7 Hz, J = 1.2 Hz, 1 H, C$H_{thiophene}$), 6.92 (dd, ^3J = 5.2 Hz, J = 3.7 Hz, 1 H, C$H_{thiophene}$), 2.62–2.56 (m, 1 H, CH), 1.90–1.84 (m, 2 H, CH_2), 1.79–1.68 (m, 2 H, CH_2), 1.57–1.48 (m, 4 H, CH_2), 1.37–1.30 (m, 4 H, CH_2); ^{13}C{^{1}H} NMR (125.77 MHz, $CDCl_3$) δ = 130.8, 126.7, 125.8, 124.3, 98.4, 73.6, 32.4, 29.9, 25.9, 24.9; HRMS calcd. for $C_{12}H_{14}S$: 190.0817, found 190.07977.

1-Methylsulfanyl-4-(4′-methoxy-phenylethynyl)-benzene (4r)

The crude product was purified *via* column chromatography on silica (cyclohexane: EtOAc = 100: 1). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.45 (d, ^3J = 9.0 Hz, 2 H, CH_{ar}), 7.42 (d, ^3J = 8.5 Hz, 2 H, CH_{ar}), 7.20 (d, ^3J = 8.5 Hz, 2 H, CH_{ar}), 6.87 (d, ^3J = 9.0 Hz, 2 H, CH_{ar}), 3.82 (s, 3 H, OCH_3), 2.49 (s, 3 H, SCH_3); ^{13}C{^{1}H} NMR (125.77 MHz, $CDCl_3$) δ = 158.6, 137.8,

132.0, 130.7, 125.0, 119.0, 114.4, 113.0, 88.5, 86.8, 54.3, 14.5; HRMS calcd. for $C_{16}H_{14}OS$: 254.0766, found 254.07671.

2-(4-Methylsulfanyl-phenylethynyl)-thiophene (4s)

The crude product was purified *via* column chromatography on silica (cyclohexane : EtOAc = 100 : 1). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.41 (d, ^3J = 8.4 Hz, 2 H, CH_{ar}), 7.27 (dd, ^3J = 5.1 Hz, J = 1.2 Hz, 1 H, C$H_{thiophene}$), 7.26 (dd, ^3J = 3.8 Hz, J = 1.3 Hz, 1 H, C$H_{thiophene}$), 7.19 (d, ^3J = 8.4 Hz, 2 H, CH_{ar}), 7.00 (dd, ^3J = 5.1 Hz, ^3J = 3.8 Hz, 1 H, C$H_{thiophene}$), 2.48 (s, 3 H, SCH_3); ^{13}C{^{1}H} NMR (125.77 MHz, $CDCl_3$) δ = 140.0, 132.2, 132.0, 127.6, 127.5, 126.3, 123.8, 119.6, 93.3, 83.1, 15.7; HRMS calcd. for $C_{13}H_{10}S_2$: 230.0225, found 230.02168.

2-Thiophen-2-ylethynyl-phenylamine (4u)

The crude product was purified *via* column chromatography on silica (cyclohexane : EtOAc : NEt_3 = 9 : 1 : 1). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.33 (dd, ^3J = 8.0 Hz, J = 1.5 Hz, 1 H, CH_{ar}), 7.27 (dd, ^3J = 5.1 Hz, J = 1.2 Hz, 1 H, C$H_{thiophene}$), 7.25 (dd, ^3J = 3.8 Hz, J = 1.2 Hz, 1 H, C$H_{thiophene}$), 7.15–7.11 (m, 1 H, CH_{ar}), 7.00 (dd, ^3J = 5.1 Hz, ^3J = 3.8 Hz, 1 H, C$H_{thiophene}$), 6.72–6.68 (m, 2 H, CH_{ar}), 4.23 (s(br), 2 H, NH_2); ^{13}C{^{1}H} NMR (125.77 MHz, $CDCl_3$) δ = 148.0, 132.3, 131.8, 130.1, 127.3, 127.2, 123.5, 118.1, 114.5, 107.7, 89.7, 87.8; ^{15}N-NMR (50.7 MHz, $CDCl_3$) δ = −321.9; HRMS calcd. for $C_{12}H_9NS$: 199.0456, found 199.04614. ^{1}H- and ^{13}C NMR-spectra are literature consistent.[76]

1-(4-Thiophen-3-ylethynyl-phenyl)-ethanone (4v)

The crude product was purified *via* column chromatography on silica (cyclohexane : EtOAc = 10 : 1). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.92 (d, ^3J = 8.5 Hz, 2 H, CH_{ar}), 7.58 (d, ^3J = 8.5 Hz, 2 H, CH_{ar}), 7.57 (dd, J = 2.8 Hz, J = 1.1 Hz, 1 H, C$H_{thiophene}$), 7.32 (dd, ^3J = 5.0 Hz, J = 3.1 Hz, 1 H, C$H_{thiophene}$), 7.21 (dd, ^3J = 5.0 Hz, J = 1.1 Hz, 1 H, C$H_{thiophene}$), 2.60 (s, 3 H, CH_3); ^{13}C{^{1}H} NMR (125.77 MHz, $CDCl_3$) δ = 197.6, 136.6, 132.0, 130.2, 129.9, 128.7, 128.6, 126.0, 122.2, 88.6, 88.3, 27.0; HRMS calcd. for $C_{14}H_{10}OS$: 226.0453, found 226.04413.

5-Thiophen-2-ylethynyl-pyridin-2-ylamine (4w)

The crude product was purified *via* column chromatography on silica (cyclohexane : EtOAc : NEt_3 = 5 : 5 : 1). ^{1}H NMR (500 MHz, $DMSO_{d6}$) δ = 8.11 (dd, J = 2.4 Hz, J = 0.8 Hz, 1 H, CH_{ar}), 7.58 (dd, ^3J = 5.4 Hz, J = 1.2 Hz, 1 H, C$H_{thiophene}$), 7.49 (dd, ^3J = 8.6 Hz, J = 2.3 Hz, 1 H, CH_{ar}), 7.31 (dd, ^3J = 3.6 Hz, J = 1.2 Hz, 1 H, C$H_{thiophene}$), 7.08 (dd, ^3J = 5.4 Hz, ^3J = 3.6 Hz, 1 H, C$H_{thiophene}$), 6.46 (dd, ^3J = 8.6 Hz, J = 0.8 Hz, 1 H, CH_{ar}), 6.45 (s(br), 2 H, NH_2); ^{13}C{^{1}H} NMR (125.77 MHz, $CDCl_3$) δ = 159.7, 151.5, 139.6, 132.0, 128.4, 128.0, 123.0, 108.0, 106.0, 92.1, 82.5; ^{15}N-NMR (50.7 MHz, $CDCl_3$) δ = −113.6 (Pyr-*N*), −299.7 (*N*H$_2$); HRMS calcd. for $C_{11}H_8N_2S$: 200.0409, found 200.03900.

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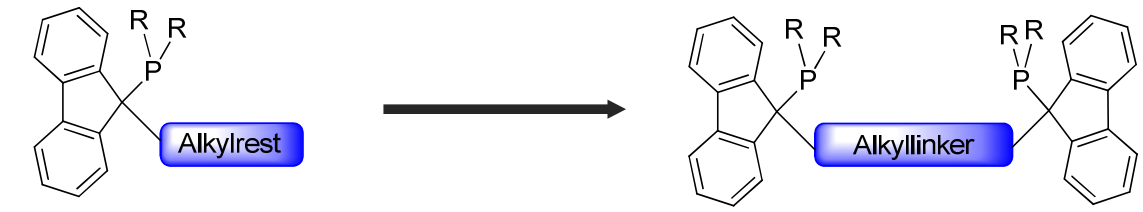
4.8. Synthese bidentater Difluorenyldiphosphine und Untersuchung ihrer katalytischen Aktivität in Pd-Kreuzkupplungen

Der Inhalt dieses Kapitels wurde bereits zur Publikation angenommen:

Christoph A. Fleckenstein, Herbert Plenio, *"Pd-Complexes of Bidentate Fluorenylphosphines and the Influence of the Bridging Unit on Pd-Catalyzed Cross Coupling Reactions"*, *Organometallics*, **2008**, zur Publikation angenommen.

Die bisher im Rahmen dieser Arbeit vorgestellten Fluorenyldialkylphosphine konnten in Form ihrer Pd-Komplexe als hochaktive Katalysatoren für Suzuki-, Sonogashira- oder Buchwald-Hartwig-Kupplungen eingesetzt werden. Als entscheidend für eine gute Aktivität der einzähnigen Phosphinliganden wurde die Funktionalisierung der Position 9 am Fluoren mit einem *n*-Alkylrest erkannt. Die hohe chemische Flexibilität des Fluorenbausteins erlaubt es des Weiteren, über diesen Alkylrest zwei 9-Phosphinofluorenylreste zu verbrücken und so zweizähnige Liganden des Fluorenyldialkylphosphintyps zu erhalten (Abb. 68).



Fluorenyldialkylphosphin
(einzähnig)

Difluorenyldiphosphin
(zweizähnig)

Abb. 68. Entwicklung der Difluorenyldiphosphine.

Diese Synthese gelang analog zur bekannten Fluorenyldialkylphosphinsynthese, ausgehend von leicht zugänglichen Difluorenylalkanen:

1.) doppelte Deprotonierung der entsprechenden Difluorenylalkane
2.) Reaktion der Fluorenyliumdianionen mit Dicyclohexylchlorphosphin
3.) Protonierung der Phosphine mit HBF_4

Auf diese Weise gelang die Darstellung sieben verschiedener, sich durch die Länge des Alkyllinkers unterscheidender Difluorenyldiphosphine als luftstabile Phosphoniumtetrafluoroborate.

Die *in situ* gebildeten Palladiumkomplexe der einzelnen Diphosphine wurden in

- Buchwald-Hartwig-Aminierungen
- Suzuki-Kupplungen und
- Sonogashira-Kupplungen

auf ihre Aktivität hin getestet und mit den Aktivitäten analoger Monophosphinkomplexe des Fluorenyltyps verglichen. Wie erwartet, lässt sich die katalytische Aktivität über die Länge und Natur der verbrückenden Einheit modulieren. In Suzuki- und Aminierungsscreenings mit Brom- und Chloraromaten kann für Pd-Komplexe der Difluorenyldiphosphine mit kurzer verbrückender Einheit eine höhere katalytische Aktivität als mit vergleichbaren Fluorenylmonophosphinen festgestellt werden. In der Sonogashira-Reaktion zeigen sich die zweizähnigen Liganden gegenüber den Monophosphinen klar unterlegen.

Pd-complexes of bidentate Fluorenylphosphines and the Influence of the bridging Unit on Pd-catalyzed Cross Coupling Reactions

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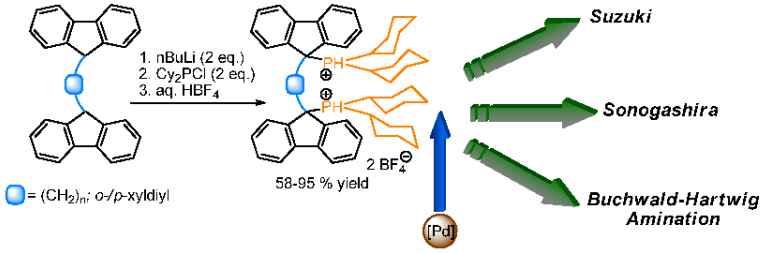


Abstract. Seven new bidentate phosphine ligands, in which two (9-(dicyclohexylphosphino)-fluoren-9'-yl) units are bridged with *n*-alkanediyl- (C_1-C_5) or *o*/*m*-xylenediyl linkers were synthesized and characterized as the respective air stable phosphonium salts. Pd complexes of the new bidentate ligands proved to be highly active catalysts for Buchwald-Hartwig-amination, Suzuki- and Sonogashira-coupling using aryl bromides and –chlorides as substrates. A study comparing the catalytic activity of the Pd complexes of the bidentate phosphine ligands with those of closely related monodentate fluorenyl phosphines gave insights into the influence of the various bridging units on the catalytic transformations. In Suzuki- and amination reactions the diphosphine **2b** with the shortest linker, -CH_2- unit, turned out to be by far the best ligand. In the Sonogashira-coupling monodentate phosphines rendered the most active Pd catalysts, while **2b** fails.

Introduction

Pd mediated cross coupling reactions are powerful tools for the formation of C-C and C-N bonds and are applied both in chemical laboratories and process development.[1-6] Of those reactions Buchwald-Hartwig amination,[7,8] Suzuki cross coupling,[9-12] Sonogashira alkynylation,[13-15] and Heck coupling,[16] are of special importance.

The most common ligand in the early days of cross coupling chemistry was Ph_3P in complexes such as $(Ph_3P)_2PdCl_2$ or $Pd(PPh_3)_4$.[11,13,14,17-19] Even though the role of increased steric bulk was recognized by Heck in 1983, when using P(*o*-tolyl)$_3$ as a ligand,[20] the Ph_3P

continued to dominate. Later the discovery by Beller and Herrmann et al. of the unique catalytic activity of a well-known dimeric complex $Pd_2(P(o\text{-}Tol)_3)_2(OAc)_2$, set a milestone in palladium catalysis.[21] A paradigm shift occurred in the mid 1990's when PPh_3 was replaced with the bulkier and more electron donating trialkylphosphines Cy_3P and $t Bu_3P$,[22] observing hitherto unprecedented catalytic activities in reactions of the amination-,[23-26] Suzuki-[27] and Sonogashira[28] type. Hartwig et al. convincingly demonstrated the advantages of sterically demanding and electron-rich phosphines.[29,30]

Since then a plethora of phosphine ligands (and numerous other classes of ligands, most notably NHC ligands)[31,32] have been developed, which enable coupling reactions at much lower catalyst loading compared to Pd-PPh_3 complexes. In figure 1 a few established representatives of modern monophosphine ligands are summarized.

The trialkylphosphine $t Bu_3P$ (**L1,** figure 1) represents a non-proprietary, highly active phosphine ligand for a broad range of Pd mediated cross couplings,[33] but lacks facile tuneability. The Beller group and us reported on the use of $(1\text{-}Ad)_2PR$ (1-Ad = 1-adamantyl) (**L2a**, **L2b**) ligands for Pd catalysis with remarkable activities in amination, Sonogashira- and Suzuki coupling.[34-43] Bulky biarylphosphines like **L3** and its derivatives developed by Buchwald et al. turned out to be outstanding ligands for Buchwald-Hartwig amination, Suzuki coupling and many other Pd catalyzed reactions.[8,44-50] The related phosphino-*N*-arylpyrrole family was built by Singer et al.[51-53] and subsequently modified to the similar highly active and easily accessible **L4** class by Beller and coworkers.[54-58] Q-Phos (**L5**), which has a ferrocene backbone, was developed by Hartwig and coworkers and is suitable for Pd mediated etherifications, aminations and arylations of aryl chlorides under mild conditions.[59-63.]

Recognizing the high catalytic activity, but inherent inflexibility of *tert*Bu_3P (**L1**), we recently developed the class of fluorenyldialkylphosphines **(L6)** whose Pd complexes display excellent activities in various cross coupling reactions and can be easily modified – also for use in water as the solvent.[64-70]

Bi- or polydentate phosphines are frequently used in Pd catalyzed cross coupling reactions, even though they were initially considered as the inferior choice.[16] However, especially in amination reactions chelating diphosphines like BINAP (**L8**, figure 2), Xantphos (**L9**) or DPPF (**L10a**) show excellent activities for aryl bromide and –chloride conversions.[7,71-75] Unfortunately there is no clear answer as to whether mono- or bidentates are more suitable in amination reactions. Although comprehensive mechanistic studies for amination reactions with Pd/monophosphine systems like Pd/$t Bu_3P$,[76] Pd/biarylphosphine[77] or with Pd/bidentate systems like Pd/BINAP[78-80] were performed, it is not well understood, why and when bidentate phosphines perform better than monophosphine ligands.

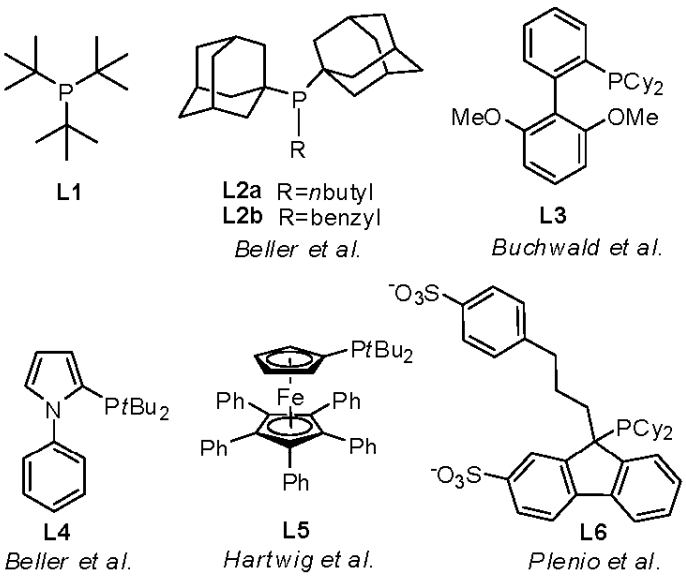


Figure 1. *Selected active monodentate phosphines for Pd mediated C-C and C-N cross coupling reactions.*

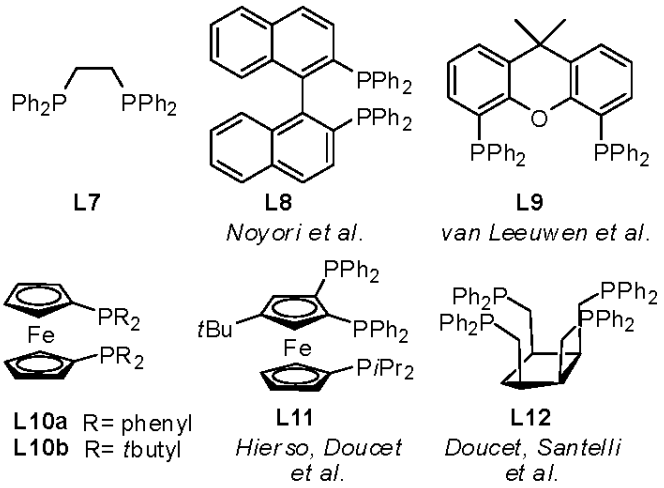


Figure 2. *Selected active polydentate phosphine ligands for Pd mediated C-C and C-N cross coupling reactions.*

Despite the popularity of monodentate phosphines there are numerous examples, where bidentates appear to perform better than monodentates.[81-84] As an example, the amination of 9-benzyl-6-bromo-1,2,3,4-tetrahydrocarbazol-1-one with 4-methylbenzamide results in 82 % yield with 1 mol % of a Pd/Xantphos catalyst; under the same reaction conditions biphenyl-di*tert*butylphosphine only affords 16 % conversion.[85] Notoriously difficult substrates like nucleosides are efficiently aminated with 3-methylindole using 5 mol% PdOAc/Xantphos affording 69 % yield whereas 2-(dicyclohexylphosphinyl)-2'-(*N,N*-dimethylamino)-1,1'-biphenyl ligands proved to be inefficient.[82]

BINAP was reported to be an useful ligand for the amination of 1,8-dichloroanthracene while sterically demanding monophosphines tBu$_3$P and Cy$_3$P are poor performers.[86] Even the simple chelating diphosphine DPPE (**L7**) may deliver remarkable results in the amination of 2-anilino-3-chloro-1,4-naphthoquinone with 4-chloroaniline[87] or other Pd mediated arylation reactions.[88]

Bidentate phosphines also form active Pd complexes for Suzuki couplings[89-92] and are well established in the Novartis Discodermolide synthesis.[93] Ostentatiously, the classic bidentates BINAP and DPPF proved to be the better choice, when heteroaryl chlorides or bromides such as chloroquinoline[94] or bromoimidazole[95] were subjected to Suzuki couplings. Pd complexes with the sterically demanding 1,1'-Fc(PtBu$_2$)$_2$ (D-t-BPF) (**L10b**) were found to be active catalysts for Suzuki arylation of aminochloropyrimidines while various monodentates such as the Buchwald biarylphosphines or tBu$_3$P failed.[96] Bidentate ligands are reported to enable Sonogashira cross coupling reactions, using Cu(I) as a co-catalyst. The reported catalytic activity of the respective Pd complexes[97,98] is clearly inferior to that of potent monophosphine systems,[35,45,64,99,100] however, with copper-free protocols good results were reported on coupling N-heteroaryl chlorides using BINAP[101] or bisdiphenylphosphinebutane (dppb). With arylsulfonate substrates, bidentate phosphines often appear to be the better choice: aryl nonaflates are efficiently aminated using Pd/Xantphos as catalyst;[102] the carbonylation of various aryltosylates and –mesylates was very recently reported by the Buchwald group utilizing Pd(OAc)$_2$ with bisdicyclohexylphosphinopropane.[103] In addition to the bidentate phosphine ligands, a few polydentate ligands have been applied of which Tedicyp (**L12**) by Doucet and Santelli may be the most prominent ones. Tedicyp is powerful in Sonogashira and Suzuki couplings of heteroaryl halides[104,105] or heteroboronic acids.[106,107]

With diphosphines steric bulk, electronic properties and the bite angle have to be taken into account. Although preliminary studies concerning the correlation between bite angle and catalytic activity of Pd complexes have been made,[108,109] there is no clear rule as to which distance between the donor atoms is ideal.[75] Recently the Wills' group tested a number of bidentate ligands in Suzuki, Sonogashira and amination reactions, to observe drastic effects on catalytic activity depending on the lengths of the bridging unit.[110] In order to get a better idea of the influence of the donor atom separation in electron rich and sterically demanding diphosphine ligands on the catalytic properties, we decided to synthesize a number of bidentate fluorenyldialkylphosphine with variable length and nature of the bridging unit.

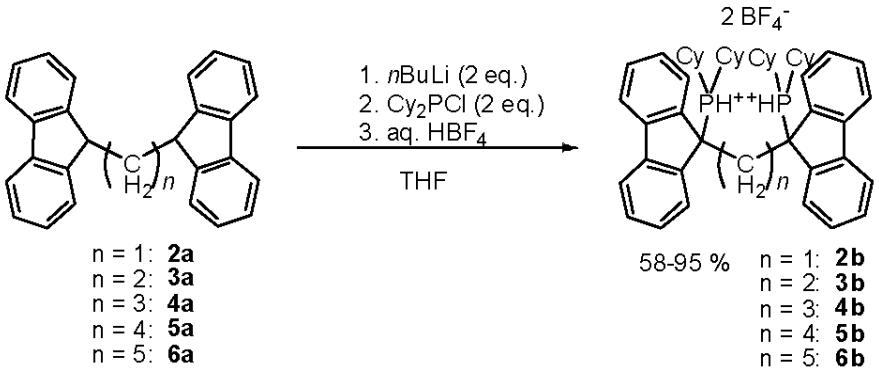
Results and Discussion

Synthesis of Ligands. In order to prepare bidentate fluorenyldialkylphosphines, we first synthesized a number of alkanediyl- and xylenediyl linked difluorenes (**2a**-**8a**). Due to its high reactivity the 9-position of fluorene serves as the anchor for the respective linkers. Difluoren-9-yl-methane **2a** was conveniently available from **1** and paraformaldehyde in 52 %

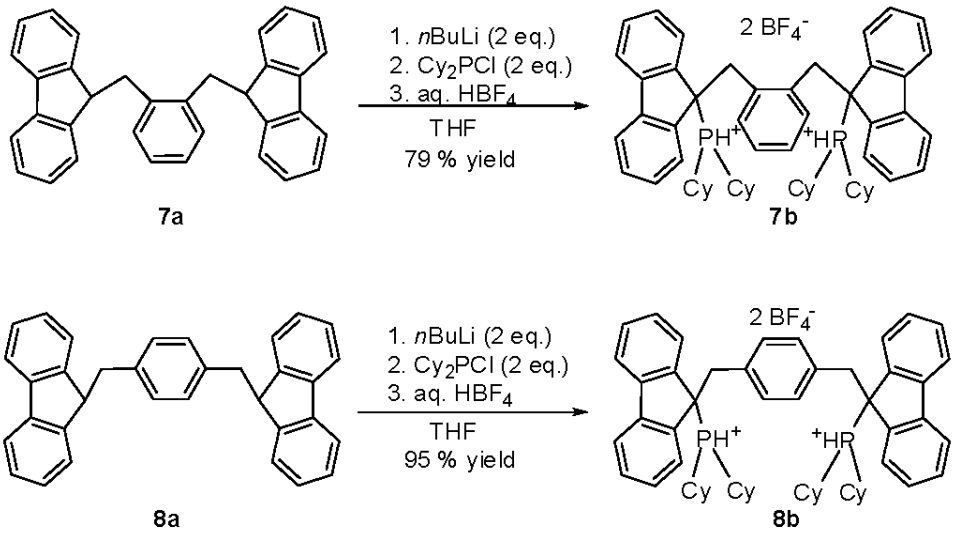
yield utilizing a slightly modified reaction protocol originally reported by Resconi et al.[111] Difluorenes **3a**, **4a**, **7a** and **8a** were obtained by stoichiometric deprotonation of **1** with *n*BuLi and subsequent quenching of the fluorenyl anion with the respective α,ω-alkyldibromide in 44-75 % yield. *n*Pentyl- and *n*butyl linked difluorenes **5a** and **6a** were conveniently prepared in 45-47 % yield by KOH catalyzed condensation of fluorene (**1**) with 1,4-butanediol or 1,5-pentanediol at elevated temperatures.[112] Due to the lower boiling points of the respective glycols, this route turned out to be inconvenient for formation of the respective difluorenes with shorter linkers.

The respective difluorenes **2a**-**8a** were doubly deprotonated with *n*BuLi and reacted with two equivalents of Cy_2PCl to obtain the respective bidentate phosphines **2b** – **8b** (scheme 2). Subsequent treatment of the reaction mixture with aq. HBF_4 led to the precipitation of the respective air stable diphosphonium salts (**2b**-**6b**)· 2 H^+ (scheme 1) and **7b**· 2 H^+ and **8b**· 2 H^+ (scheme 2) in good yields and high purities. The synthesis of the CH_2 –bridged and sterically congested diphosphine **2b** requires elevated temperatures (50 °C) to effect the full conversion of the reactants.

The phosphines synthesized here are potential chelating ligands. Whether chelated metal complexes represent the catalytically active Pd species remains unclear. It is known that especially the long chain linked diphosphines are variable in their coordination chemistry. McAuliffe et al.,[113] Shaw et al.,[114] and Sijbesma/Paulusse[115] reported on the formation of cis- and trans-configured Pd complexes and on polymeric species.



Scheme 1. *Synthesis of the nalkanediyl linked diphosphines* ***2b-6b****. Reagents and conditions: 1. nBuLi, THF, 0 °C; 2.* Cy_2PCl*, 0 °C; 3. aq.* HBF_4*.*



Scheme 2. *Synthesis of the xylendiyl linked diphosphines* ***7b, 8b****. Reagents and conditions: 1. nBuLi, THF, 0°C; 2. Cy_2PCl, 0 °C; 3. aq. HBF_4.*

Depicted in figure 2 are two related monodentate fluorenylphosphines **A** and **B** used as catalysis benchmarks.

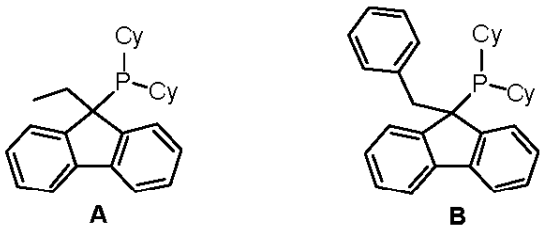


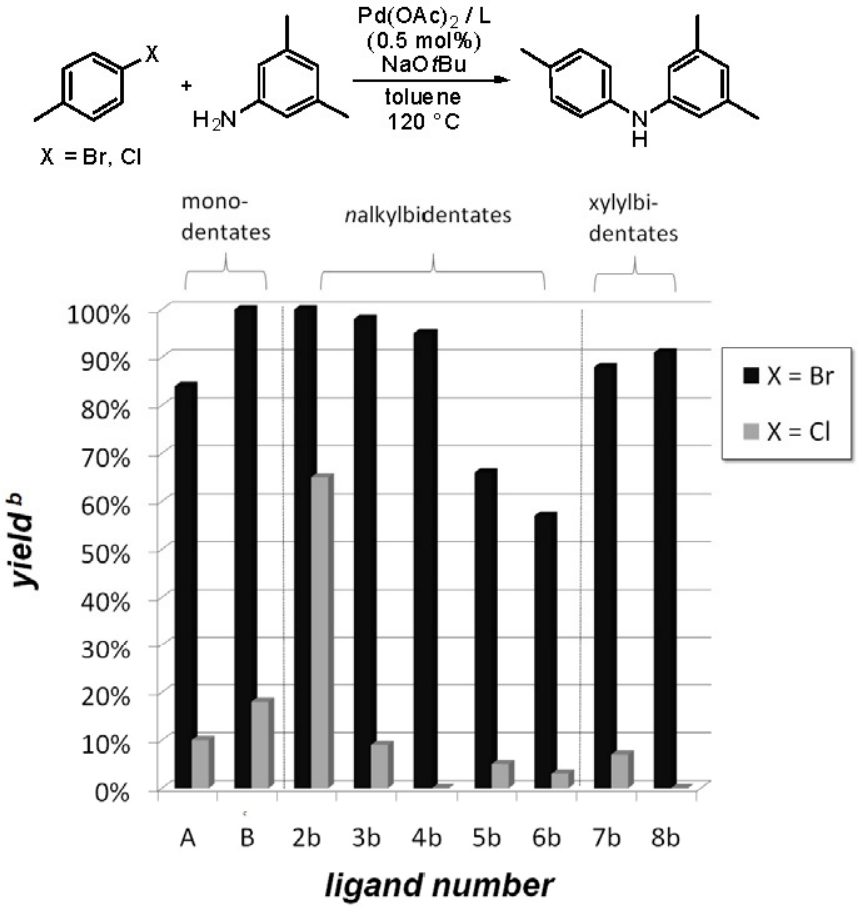
Figure 2. *9-Ethylfluorenyl-dicyclohexyl-phosphine (**A**) and 9-benzylfluorenyl-dicyclohexyl-phosphine (**B**).*

Cross coupling reactions. With this set of ligands we tested Pd complexes of the bidentate phosphines **2b**-**8b** in various cross-coupling reactions and compared their catalytic efficiency with those of the Pd-complexes with the monodentates **A** and **B**. In the Buchwald-Hartwig amination of 4-bromotoluene with 3,5-dimethylaniline in toluene and NaO*t*Bu as a base, all Pd catalysts were formed *in situ* from $Pd(OAc)_2$ and the respective phosphonium salts. The catalysts showed high activity and led to good conversions (figure 3). However, starting with full conversion for a catalyst loading of 0.5 mol % Pd/**2b,** a continuous decrease of activity could be observed with increased length of the *n*alkyl linker. With Pd/**6b** only a 57 % yield was observed.

For a more detailed understanding a related set of screening experiments was done with *p*chlorotoluene. Using ligand **2b** led to significant higher conversions (65 %) than with all other ligands. With Pd/**2b** as a catalyst the amination turned out to be highly selective towards the secondary aniline, whereas significant amounts of tertiary aniline were detected with the monodentate system Pd/**B**.[116] The remaining diphosphines (**3b**-**8b**) perform poorly compared

to the monodentates **A** and **B**. These results are surprising, because normally diphosphines with well separated donor atoms render high catalytic activity in amination reactions whereas diphosphines with small bite angles such as dppe or dppp were reported to fail.[117,75,118]

Figure 3. Buchwald-Hartwig Amination.[a]

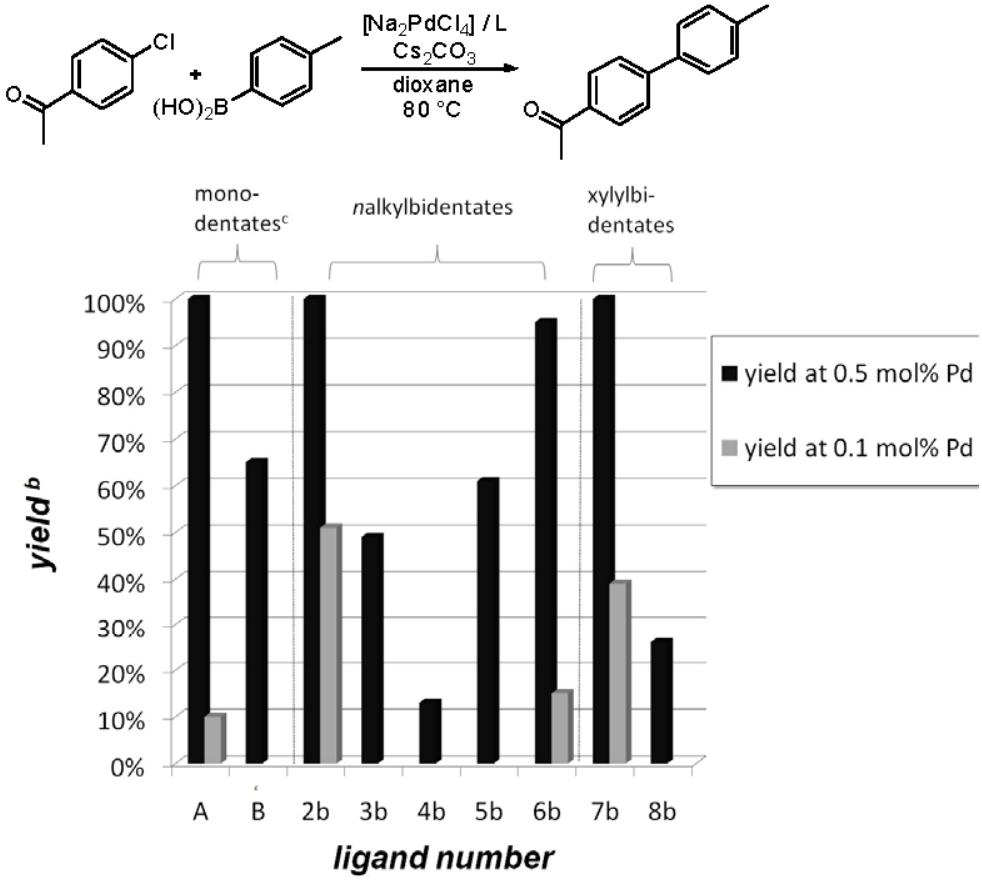


[a] Reaction conditions: 1.0 mmol aryl halide, 1.5 mmol aniline, 2.0 mmol NaO*t*Bu, 0.5 mol% $Pd(OAc)_2$ 0.5 mol% ligand (in case of monodentate ligands **A** and **B** 1 mol% ligand were used), toluene (5 mL ml), 120 °C, 12 h. [b] Average of two runs, determined by GC using heptadecane as internal standard. [c] formation of significant amounts (4 %) of tertiary aniline was observed.

Next, we applied the various *in situ* formed Pd complexes in Suzuki couplings by reacting *p*chloroacetophenone with *p*tolylboronic acid. Using 0.5 mol% of the respective catalysts, only the bidentates **2b** and **6b** showed high activities (figure 4). The diphosphines with an intermediate number of atoms separating the two donor atom are less efficient. **5b** and **6b** behave similar to monodentate ligands. In order to better understanding which catalyst performs best, the four most active complexes Pd/**A**, Pd/**2b**, Pd/**6b** and Pd/**7b** were subjected to a second screening. Here less catalyst (0.1 mol%) was applied, while maintaining all other reaction parameters. The three selected bidentate phosphine ligands possess significantly

higher catalytic activities than the monodentate ligand **A**. The diphosphine **2b** bearing the shortest linker proved to be most active one - more than five times higher than the monodentate ligand **A.** Thus among the phosphines tested here, **2b** turned out to be the most active ligand.

***Figure 4**. Suzuki Cross Coupling.*[a]



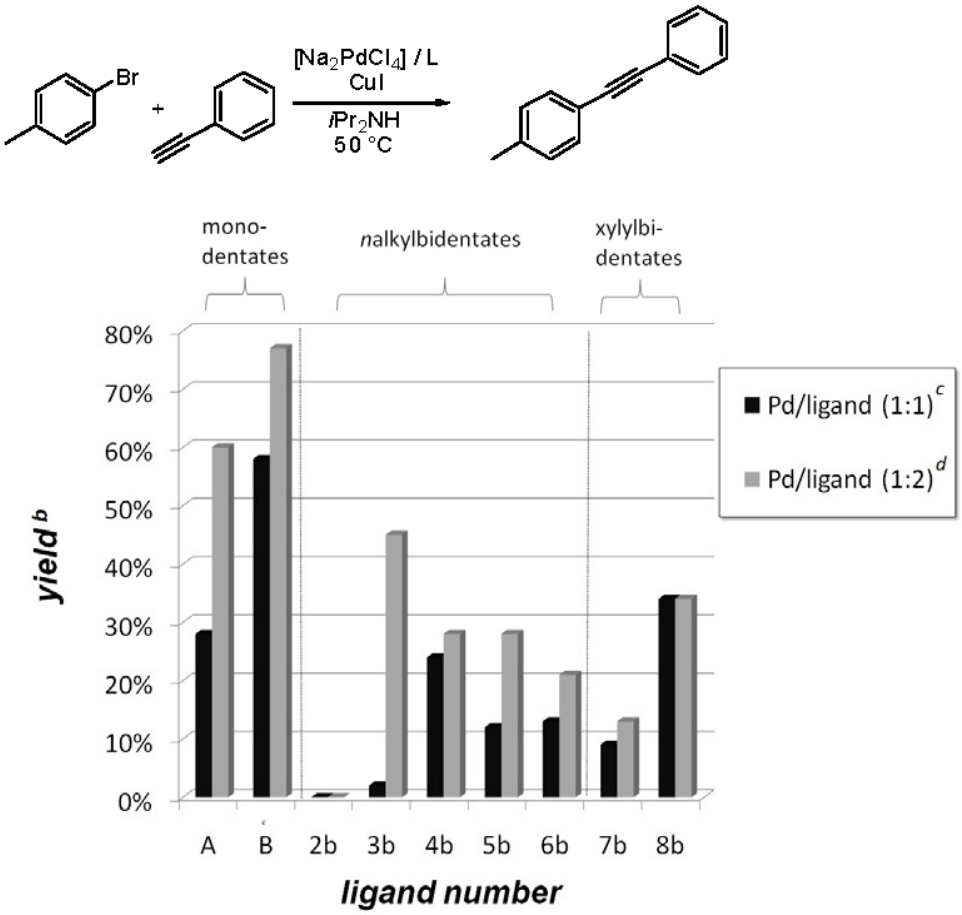
[a] Reaction conditions: 1.0 equiv. *p*chloroacetophenone, 1.5 equiv. tolylboronic acid, 2.0 equiv. Cs_2CO_3, dioxane (5.0 ml $mmol^{-1}$), cat.: the respective volume of aqueous catalyst stock solution (c_{Pd}=0.005 mol/L, $[Na_2PdCl_4]$ / ligand: 1:1. 80 °C, 15 h. [b] Average of two runs, determined by GC using heptadecane as internal standard. [c] For monodentate ligands **A** and **B** the Pd / ligand ratio was 1:2 in the catalyst stock solution.

Finally, we applied the various mono- and bidentate phosphines in the Sonogashira coupling of 4-bromotoluene with phenylacetylene using diisopropylamine as solvent and CuI as cocatalyst at 50 °C. Fluorenyldialkylphosphines are known to be highly active in Sonogashira coupling of aryl bromides,[64] the required low catalyst concentrations (0.00667 mol% Pd) could be handled easily by application of premixed "ready made catalyst".[119] In two independent screening reactions we applied an *in situ* formed catalyst consisting of $[Na_2PdCl_4]$, ligand and CuI in 4:4:3 and 4:8:3 ratio, respectively (figure 5). In general,

Sonogashira reactions effected by a catalyst mixture with a higher phosphine ratio (Pd/L 1:2) led to significantly higher yield.

We were surprised to learn that ligand **2b**, which was extremely useful in Suzuki and amination reactions failed in the Sonogashira coupling. All other diphosphines, provide medium catalytic activity, independent of the nature of the bridging unit. Catalysts [Pd/**A**] and [Pd/**B**] derived from monodentate ligands are by far the most active catalysts. Complex [Pd/**8b**] shows activity comparable to that of the mondentates and phosphine **B**. We ascribe the lower activity of the bidentate ligands, especially of **2b** in Sonogashira cross coupling, to a strong chelation and thus inhibition of the copper cocatalyst whose presence is essential for these high activity catalysts. Consequently, optimization of catalysts for Sonogashira cross coupling reactions must follow other principles than Suzuki coupling or amination.

Figure 5. Sonogashira Cross Coupling.[a]



[a]Reaction conditions: 10 equiv. 4-bromotoluene, 11 mmol phenylacetylene, 10 mL iPr$_2$NH, cat.: the respective amount of ready made catalyst, triturated with iPr$_2$NH$_2$Br, (cat.-loading: 0.00667 mol%), 50 °C, 24 h. [b] determined via GC, external calibration calculating with the response factors of analytically pure samples of starting material (4-bromotoluene) and product. [c] catalyst composition: [Na$_2$PdCl$_4$]/ligand/CuI (4:4:3). [d] catalyst composition: [Na$_2$PdCl$_4$]/ligand/CuI (4:8:3).

Summary and Conclusion

Motivated by the success of monodentate fluorenyldialkylphosphines ligands in Pd mediated cross coupling reactions, we synthesized seven new *n*alkanediyl- and xylenediyl linked fluorenyldiphosphines **2b-8b**. The new diphosphines were tested in Buchwald-Hartwig amination, Suzuki- and Sonogashira reactions using aryl bromides and –chlorides as substrates. The catalytic activity of the Pd complexes is systematically modulated, depending on the nature of the bridge linking the two P donors. Based on our study we can draw the following conclusions:

a) In Buchwald-Hartwig amination and in Suzuki reactions Pd complexes of diphosphines with short chain linked P donors display superior catalytic activity compared to complexes of monophosphines. The fluorenylphosphines **2b** with a CH_2 linker renders a Pd complex of excellent activity.

b) Pd complexes of diphosphines with distant P donors are comparable to those of the respective monodentate ligands.

c) In Sonogashira coupling reactions monophosphines appear to be superior to diphosphines - especially ligand **2b** with excellent properties in amination and Suzuki reactions fails in the Sonogashira coupling.

Acknowledgements

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Supporting Information Available: Contains the full set of ^{1}H, ^{13}C, ^{31}P and ^{15}N NMR spectra of all compounds synthesized. This material is available free of charge via the Internet at http://pubs.acs.org.

General Experimental

All chemicals were purchased as reagent grade from commercial suppliers and used without further purification, unless otherwise noted. Toluene was freshly distilled over sodium, dioxane was dried over CaH_2, HN*i*Pr$_2$ was dried over KOH. Solvents used in cross coupling experiments were deaerated via freeze and thaw technique (2x). Cs_2CO_3 (99.5 %) was purchased from *Chemetall*, NaO*t*Bu (98 %) was purchased from *Acros*. All "phosphines" mentioned in this publication were used as their air stable phosphonium salts and deprotonated *in situ* during the catalyst preparation. All experiments were carried out under an argon atmosphere, unless otherwise noted. ^{1}H NMR, ^{13}C NMR, ^{31}P NMR and ^{15}N NMR spectra were recorded on a Bruker DRX 500 at 500 MHz, 125.75 MHz, 202.46 MHz and 50.69 MHz, respectively at 293 K. The chemical shifts are given in parts per million (ppm) on

the delta scale (δ) and are referenced to tetramethylsilane (δ= 0 ppm), ^{1}H NMR, 65% aq. H_3PO_4. (δ= 0 ppm), ^{31}P NMR and nitromethane (δ= 0 ppm), ^{15}N NMR. Abbreviations for NMR data: s = singlet; d = doublet; t = triplet; q = quartet; qi = quintet; dd = doublet of doublets; dt = doublet of triplets; dq = doublet of quartets; tt = triplet of triplets; m = multiplet. Mass spectra were recorded on a Finnigan MAT 95 magnetic sector spectrometer. Melting points were determined on a Büchi Type B-540 melting point apparatus and corrected versus caffeine (p.a. quality, m.p. 236.1 °C) as standard.

Thin layer chromatography (TLC) was performed using Fluka silica gel 60 F 254 (0.2 mm) on Al-plates. Silica gel columns for chromatography were prepared with *E. Merck* silica gel 60 (0.063-0.20 mesh ASTM). GC experiments were run on a Clarus 500 GC with autosampler and FID detector. Column: Varian CP-Sil 8 CB (l = 15 m, d_i = 0.25 mm, d_F = 1.0 µm), N_2 (flow: 17 cm/sec; split 1:50); Injector-temperature: 270 °C, detector temperature: 350 °C. Temperature program: isotherm 150 °C for 5 min, heating to 300 °C with 25 °C/min, isotherm for 15 min.

Difluoren-9-yl-methane (2a): In a 250 mL Schlenk-flask fluorene (15 g, 90.2 mmol) was dissolved in dry DMF (150 mL). KO*t*Bu (12.15 g, 108 mmol) was added and the resulting red reaction mixture was stirred at ambient temperature for 12 h, then for additional 2 h at 70 °C. The reaction mixture was poured into water (300 mL) and extracted with THF/MTBE (1:1, 4 x 150 mL). The combined organic layers were dried over $MgSO_4$, filtered, the solvent volume reduced *in vacuo* to about 100 mL. Addition of cyclohexane (200 mL) and removal of the remaining THF via rotary evaporation afforded a slightly yellowish crude solid which was separated via suction filtration. Recrystallisation from cyclohexane (1 L) afforded **2a** as white crystals (8.1 g, 52 %). The ^{1}H- and ^{13}C NMR spectra are identical to those in the literature.[111] mp 207.5 °C (cyclohexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (d, ^{3}J = 7.6 Hz, 4 H, *CH*, ar), 7.54 (d, ^{3}J = 7.6 Hz, 4 H, *CH*, ar), 7.39 (t, ^{3}J = 7.5 Hz, 4 H, *CH*, ar), 7.27 (dt, ^{3}J = 7.5 Hz, J = 1.1 Hz, 4 H, *CH*, ar), 4.39 (t, ^{3}J = 7.5 Hz, 2 H, *H*Flu), 2.24 (t, ^{3}J = 7.6 Hz, 2 H, CH_2); ^{13}C units NMR (125.8 MHz, $CDCl_3$) δ 147.5, 141.0, 127.2, 127.0, 125.0, 120.1, 45.9, 38.8; elemental analysis calcd. (%) for $C_{27}H_{20}$: C 94.15, H 5.85; found: C 94.07, H 5.89; HRMS calcd. for $C_{27}H_{20}$: 344.1565, found 344.15884.

1,2-Difluoren-9-yl-ethane (3a): In a 500 mL Schlenk-flask fluorene (20 g, 120 mmol) was dissolved in dry THF (350 mL). *n*BuLi (50 mL, 2.5 molar solution in hexane, 125 mmol) was added to the stirred solution at -50 °C. The resulting orange solution was stirred at that temperature for 5 min, allowed to come to ambient temperature and stirred for additional 1 h. At -50 °C 1,2-dibromoethane (11.9 g, 5.46 mL, 63.5 mmol) was added to the stirred solution within 1 min via a syringe. The reaction mixture was allowed to come to ambient temperature, stirred for 1 h. The reaction mixture was evaporated in vacuo to afford a white solid residue. The solid was stirred in water/EtOH (1:1, 500 mL) for 40 min. Then the solid was separated via suction filtration and recrystallized from hot xylene (400 mL) to afford **3a**

as white crystals (10.5 g, 48.7 %). The ^{1}H- and ^{13}C NMR spectra are identical to those in the literature.[120]

mp 228.0 °C (xylene); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, ^{3}J = 7.5 Hz, 4 H, *CH*, ar), 7.38-7.34 (m, 4 H, *CH*, ar), 7.32-7.26 (m, 8 H, *CH*, ar), 3.84 (m, 2 H, *H*Flu), 1.74-1.72 (m, 4H, Flu-C*H*$_2$); ^{13}C{^{1}H} NMR (125.8 MHz, $CDCl_3$) δ 147.2, 141.7, 127.4, 127.3, 124.6, 120.2, 47.4, 27.0; elemental analysis calcd (%) for $C_{28}H_{22}$: C 93.81, H 6.19; found: C 93.72, H 6.13; HRMS calcd. for $C_{28}H_{22}$: 358.1721, found 358.17463.

1,3-Difluoren-9-yl-propane (4a): In a 500 mL Schlenk-flask fluorene (20 g, 120 mmol) was dissolved in dry THF (350 mL). *n*BuLi (50 mL, 2.5 molar solution in hexane, 125 mmol) was added to the stirred solution at -50 °C. The resulting orange solution was stirred at that temperature for 5 min, allowed to come to ambient temperature and stirred for additional 1 h. At -50 °C 1,3-dibromopropane (12.6 g, 6.38 mL, 62.6 mmol) was added to the stirred solution within 1 min via a syringe. The reaction mixture was allowed to come to ambient temperature, stirred for 1 h and then quenched with water (100 mL). After addition of MTBE (100 mL) the organic layer was separated, washed with saturated aq. $Na_2S_2O_3$-solution (100 mL) and water (100 mL), dried over $MgSO_4$, filtered and the volatiles removed in vacuo to afford crude **4a** as a white solid. The solid was dissolved in Et_2O (500 mL), *n*pentane (50 mL) was added and the solution was allowed to stand in an open 1 L Erlenmeyer-flask at room temperature. Slow evaporation of the solvent within 2 days the product afforded **4a** (16.9 g, 75 %) as pure white crystals. The ^{1}H- and ^{13}C NMR spectra are identical to those in the literature.[121]

mp 115.9 °C (Et_2O/*n*pentane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, ^{3}J = 7.6 Hz, 4 H, *CH*, ar), 7.35 (d, ^{3}J = 7.2 Hz, 4 H, *CH*, ar), 7.33 (t, ^{3}J = 7.5 Hz, 4 H, *CH*, ar), 7.24 (dt, ^{3}J = 7.4 Hz, J = 1.1 Hz, 4 H, *CH*, ar), 3.88 (t, ^{3}J = 6.2 Hz, 2 H, *H*Flu), 1.94-1.88 (m, 4 H, C*H*$_2$(propyl)), 1.35-1.27 (m, 2 H, C*H*$_2$(propyl)); ^{13}C{^{1}H} NMR (125.8 MHz, $CDCl_3$) δ 147.9, 141.5, 127.3, 127.2, 124.8, 120.2, 47.6, 33.7, 23.2; elemental analysis calcd. (%) for $C_{29}H_{24}$: C 93.51, H 6.49; found: C 93.33, H 6.50; HRMS calcd. for $C_{29}H_{24}$: 372.1878, found 372.18669.

1,4-Difluoren-9-yl-butane (5a): In a 500 mL 3-necked round-bottomed flask fitted with a mechanical stirrer, reflux condenser (Liebig-condenser) and a metal bath fluorene (100 g, 602 mmol) and potassium hydroxide (33.6 g, 600 mmol) were suspended in 1,4-butanediol (357 g, 350 mL, 3.96 mol) and stirred at 250 °C for 6 h. During the first hour unreacted fluorene sublimed in the Liebig condenser and was mechanically returned into the reaction mixture. After the reaction time the mixture was allowed to come to 80 °C and then poured into water (1.5 L) while stirring. After standing overnight the white solid that precipitated was separated via suction filtration and washed thoroughly with water (5 x 60 mL). The white solid was refluxed twice in MeOH and hot filtered to remove 4-(9*H*-fluoren-9-yl)-butan-1-ol **(5c)** byproduct. The residual solid was purified via short column chromatography (silica, 10 x 10 cm; eluent: cyclohexane/ethyl acetate (95:5)) to afford **5a** as a white solid (51 g, 45 %).

mp 161.2 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, ^{3}J = 7.5 Hz, 4 H, *CH*, ar), 7.41 (dd, ^{3}J = 7.5 Hz, J = 0.8 Hz, 4 H, *CH*, ar), 7.33 (tt, ^{3}J = 7.3 Hz, J = 0.8 Hz, 4 H, *CH*, ar), 7.26 (dt, ^{3}J = 7.4 Hz, J = 1.2 Hz, 4 H, *CH*, ar), 3.88 (t, ^{3}J = 5.8 Hz, 2 H, *H*Flu), 1.94-1.87 (m, 4H, Flu-CH_2), 1.13-1.08 (m, 4H, CH_2(butyl)); ^{13}C{^{1}H} NMR (125.8 MHz, $CDCl_3$) δ 147.4, 141.1, 126.8, 126.7, 124.3, 119.7, 47.4, 32.8, 25.9; elemental analysis calcd. (%) for $C_{30}H_{26}$: C 93.22, H 6.78; found: C 93.02, H 6.73; HRMS calcd. for $C_{30}H_{26}$: 386.2034, found 386.20289.

1,5-Difluoren-9-yl-pentane (6a): In a 500 mL 3-necked round-bottomed flask fitted with a mechanical stirrer, reflux condenser (Liebig-condenser) and a metal bath, fluorene (100 g, 602 mmol) and KOH (33.6 g, 600 mmol) were suspended in 1,5-pentanediol (368 g, 370 mL, 3.53 mol) and stirred at 250 °C for 6 h. During the first hour unreacted fluorene sublimed in the Liebig condenser and was mechanically returned into the reaction mixture. After 6 h the mixture was allowed to come to 80 °C and poured into water (1.5 L) while stirring. The product was extracted with MTBE (3 x 400 mL). The combined organic phases were dried over $MgSO_4$, filtered and the volatiles removed *in vacuo*. The residue was adsorbed on silica gel (100 g) and purified via column chromatography (silica, 20 x 10 cm; eluent: cyclohexane/ethyl acetate (95:5)) to afford **6a** as a white solid (55 g, 47 %).

mp 82.4 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, ^{3}J = 7.6 Hz, 4 H, *CH*, ar), 7.43 (d, ^{3}J = 7.6 Hz, 4 H, *CH*, ar), 7.32 (t, ^{3}J = 7.6 Hz, 4 H, *CH*, ar), 7.26 (dt, ^{3}J = 7.5 Hz, J = 1.2 Hz,4 H, *CH*, ar), 3.90 (t, ^{3}J = 5.8 Hz, 2 H, Flu-C*H*), 1.93-1.87 (m, 4 H, Flu-CH_2), 1.23-1.16 (m, 2 H, Flu-CH_2-CH_2-CH_2), 1.10-1.02 (m, 4 H, Flu-CH_2-CH_2) ^{13}C{^{1}H} NMR (125.8 MHz, $CDCl_3$) δ 147.5, 141.1, 126.8, 126.7, 124.3, 119.8, 47.3, 32.9, 30.2, 25.2; elemental analysis calcd. (%) for $C_{31}H_{28}$: C 92.95, H 7.05; found: C 92.73, H 7.04; HRMS calcd. for $C_{31}H_{28}$: 400.2191, found 400.21767.

α,α'-Difluoren-9-yl-*o*-xylene (7a): In a 500 mL Schlenk-flask fluorene (20 g, 120 mmol) was dissolved in dry THF (350 mL). *n*BuLi (50 mL, 2.5 molar solution in hexane, 125 mmol) was added to the stirred solution at -50 °C. The resulting orange solution was stirred at this temperature for 5 min, allowed to come to ambient temperature and stirred for an additional 60 min. After re-cooling to -50 °C a solution of α,α'-dibromo-*o*-xylene (16.5 g, 62.6 mmol in 50 mL dry THF) was syringed into the stirred solution within 2 min. The reaction mixture was allowed to come to ambient temperature, stirred for 1 h and then quenched with water (100 mL). The organic layer was separated, washed with saturated $Na_2S_2O_3$-solution (100 mL) and water (100 mL), dried over $MgSO_4$, filtered and the volatiles removed in vacuo to afford crude **7a** as a yellow oily residue. The residue was taken up in xylene (200 mL), after a few minutes a white precipitate was formed. The resulting suspension was stirred at ambient temperature for 1 h, the solid was isolated via suction filtration, washed with xylene (2 x 20 mL) and dried *in vacuo* (90 °C, 1 mbar) affording **7a** (11.5 g, 44 %) as pure white crystals.

mp 165.3 °C (xylene); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, ^{3}J = 7.6 Hz, 4 H, C*H*, ar), 7.38 – 7.31 (m, 4 H, C*H*, ar), 7.29 (t, ^{3}J = 7.6 Hz, 4 H, C*H*, ar), 7.13 (dt, ^{3}J = 7.5 Hz, J = 1.1 Hz,4 H, CH, ar), 7.01-6.98 (m, 4 H, C*H*, ar), 4.10 (t, ^{3}J = 8.0 Hz, 2 H, *H*Flu), 2.99 (d, ^{3}J = 8.0 Hz, 4 H, $CH_{2(benzyl)}$); $^{13}C\{^{1}H\}$ NMR (125.8 MHz, $CDCl_3$) δ 146.8, 140.6, 138.8, 130.8, 127.1, 126.6, 124.8, 119.8, 48.1, 37.2; elemental analysis calcd. (%) for $C_{34}H_{26}$: C 93.97, H 6.03; found: C 93.78, H 6.03; HRMS calcd. for $C_{34}H_{26}$: 434.2034, found 434.20710.

α,α'-Difluoren-9-yl-*p*-xylene (8a): In a 1 L Schlenk-flask fluorene (20 g, 120 mmol) was dissolved in dry THF (350 mL). *n*BuLi (50 mL, 2.5 molar solution in hexane, 125 mmol) was added to the stirred solution at -50 °C. The resulting orange solution was stirred at that temperature for 5 min, allowed to come to ambient temperature and stirred for additional 1 h. After re-cooling to -50 °C a solution of α,α'-dibromo-*p*-xylene (16.5 g, 62.6 mmol in 100 mL dry THF) was syringed into the stirred solution within 5 min. The reaction mixture was allowed to come to ambient temperature, stirred for 1 h and then quenched with water (100 mL) and MTBE (100 mL). The precipitated solid was separated via suction filtration and dissolved in hot chloroform (1 L). The product containing solution was transferred into a wide necked Erlenmeyer flask and left standing. Slow evaporation of the solvent (to a volume of 600 mL) at ambient temperature within 4 days afforded **8a** (17.6 g, 67 %) as pure white crystals. The ^{1}H- and ^{13}C NMR spectra are identical to those in the literature.[122]

mp 244.4 °C (chloroform); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (d, ^{3}J = 7.5 Hz, 4 H, *CH*, ar), 7.35 (t, ^{3}J = 7.5 Hz, 4 H, *CH*, ar), 7.23 (dt, ^{3}J = 7.5 Hz, J = 1.0 Hz,4 H, *CH*, ar), 7.18 (d, ^{3}J = 7.5 Hz, 4 H, *CH*, ar), 7.09 (s, 4 H, C*H*, $ar_{(benzyl)}$), 4.23 (t, ^{3}J = 7.5 Hz, 2 H, Flu-C*H*), 3.12 (d, ^{3}J = 7.5 Hz, 4 H, CH_2) $^{13}C\{^{1}H\}$ NMR (125.8 MHz, $CDCl_3$) δ 146.8, 140.9, 137.6, 129.4, 127.1, 126.6, 124.9, 119.8, 48.7, 39.7; elemental analysis calcd. (%) for $C_{34}H_{26}$: C 93.97, H 6.03; found: C 93.69, H 6.10; HRMS calcd. for $C_{34}H_{26}$: 434.2034, found 434.20478.

*General procedure for synthesis of phosphines **2b-8b**:*

In a 500 mL Schlenk-flask the respective difluorene **2a-8a** (1.0 eq.) was dissolved in dry THF (150 mL). At 0 °C (ice/water cooling) *n*BuLi (2.0 eq., 2.5 M solution in hexane) was added dropwise within 2 min and the resulting red reaction mixture was stirred for additional 2 h at ambient temperature. Then the mixture was cooled to 0 °C and Cy_2PCl (~2.0 eq.) was added until the red color of the solution disappeared. After stirring for 10 min at ambient temperature aqueous HBF_4 (48%, 2.5 eq.) was added while stirring. Additional HBF_4 (2 M in water, 25 mL) and MTBE (100 mL) were added to precipitate product. Filtration and drying *in vacuo* (1 mbar, 60 °C) afforded the respective phosphonium salts **2b-8b** as white powders in 58-95 % yield.

1,1-Bis-(9-(dicyclohexylphosphinotetrafluoroborate)-fluorenyl)-methane (2b): Difluorenylmethane **(2a)** (2.5 g, 7.26 mmol); *n*BuLi (5.81 mL, 14.5 mmol); Cy_2PCl (3.38 g, 14.5 mmol) afforded **2b** (3.9 g, 58%) as a white powder. *Note:* Reaction temperature after addition

of Cy_2PCl was raised up to 50 °C for 20 min. mp 202 °C (decomp.); ^1H NMR (500 MHz, $CDCl_3$) δ 7.88 (d, ^3J = 7.6 Hz, 4 H, *CH*, ar), 7.77 (t, ^3J = 7.6 Hz, 4 H, *CH*, ar), 7.56 (t, ^3J = 7.6 Hz, 4 H, *CH*, ar), 7.47 (dt, ^3J = 7.6 Hz, *J* = 1.0 Hz, 4 H, *CH*, ar), 6.69 (d, ^1J = 487 Hz, 2 H, P*H*), 5.22 (d, $^3J(P,H)$ = 16.7 Hz, 2 H, CH_2), 2.23-2.11 (m, 4 H, PC*H*), 1.91-1.77 (m, 8 H, Cy-CH_2), 1.76-1.61 (m, 8 H, Cy-CH_2), 1.58-1.39 (m, 8 H, Cy-CH_2), 1.32-1.11 (m, 16 H, Cy-CH_2); $^{13}C\{^1H\}$ NMR (125.8 MHz, $CDCl_3$) δ 141.6 (d, *J(P,C)* = 4.6 Hz), 135.9 (d, *J(P,C)* = 5.3 Hz), 130.0 (d, *J(P,C)* = 2.1 Hz), 128.8 (d, *J(P,C)* = 2.2 Hz), 125.6, (d, *J(P,C)* = 3.4 Hz), 121.2, 36.4 (d, *J(P,C)* = 38.5 Hz), 28.5, 28.2, 27.5 (d, *J(P,C)* = 10.0 Hz), 27.5 (d, *J(P,C)* = 2.2 Hz), 26.4 (d, *J(P,C)* = 13.3 Hz), 26.1 (d, *J(P,C)* = 13.2 Hz), 24.7; $^{31}P\{^1H\}$ NMR (202.5 MHz, $CDCl_3$) δ 28.7; ^{31}P NMR (202.5 MHz, $CDCl_3$) δ 28.7 (d, *J(P,H)* = 485 Hz); MS (70 eV) m/z 737.6 $[M\text{-}H^+]^+$, 541.3 $[M\text{-}PHCy_2]^+$, 363.3 $[FluPHCy_2+H]^+$.

1,2-Bis-(9-(dicyclohexylphosphinotetrafluoroborate)-fluorenyl)-ethane (3b): 1,2-Difluorenylethane **(3a)** (3.03 g, 8.44 mmol); *n*BuLi (6.75 mL, 16.9 mmol); Cy_2PCl (3.93 g, 16.9 mmol) afforded **3b** (6.6 g, 84 %) as a white powder. mp 262.5 °C (decomp.); ^1H NMR (500 MHz, $CDCl_3$) δ 7.90 (d, ^3J = 7.6 Hz, 4 H, *CH*, ar), 7.61 (t, ^3J = 7.6 Hz, 4 H, *CH*, ar), 7.56-7.47 (m, 8 H, *CH*, ar), 6.29 (d, ^1J = 477 Hz, 2 H, P*H*), 2.14-2.03 (m, 4 H, PC*H*), 1.98-1.94 (m, 4 H, Flu-CH_2), 1.65-1.51 (m, 16 H, Cy-CH_2), 1.39-1.31 (m, 4 H, Cy-CH_2), 1.20-0.90 (m, 20 H, Cy-CH_2); $^{13}C\{^1H\}$ NMR (125.8 MHz, $CDCl_3$) δ 141.1 (d, *J(P,C)* = 4.1 Hz), 138.7 (d, *J(P,C)* = 2.5 Hz), 130.8, 129.5, 125.3, (d, *J(P,C)* = 2.8 Hz), 121.4, 51.0 (d, *J(P,C)* = 34.4 Hz), 31.3, 31.0, 29.2 (d, *J(P,C)* = 2.8 Hz), 28.1 (d, *J(P,C)* = 10.6 Hz), 27.9 (d, *J(P,C)* = 2.8 Hz), 26.5 (d, *J(P,C)* = 13.1 Hz), 26.3 (d, *J(P,C)* = 13.1 Hz), 24.8; $^{31}P\{^1H\}$ NMR (202.5 MHz, $CDCl_3$) δ 33.1; ^{31}P NMR (202.5 MHz, $CDCl_3$) δ 33.1 (d, *J(P,H)* = 477 Hz); MS (70 eV) m/z 751.6 $[M\text{-}H^+]^+$, 553.4 $[M\text{-}PHCy_2\text{-}H^+]^+$.

1,3-Bis-(9-(dicyclohexylphosphinotetrafluoroborate)-fluorenyl)-propane (4b): 1,3-Difluorenylpropane **(4a)** (2.5 g, 6.71 mmol); *n*BuLi (5.37 mL, 13.42 mmol); Cy_2PCl (3.12 g, 13.42 mmol) afforded **4b** (4.99 g, 79%) as a white powder. mp 248.9-250.6 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 7.74 (d, ^3J = 7.6 Hz, 4 H, *CH*, ar), 7.62 (d, ^3J = 7.6 Hz, 4 H, *CH*, ar), 7.46 (t, ^3J = 7.6 Hz, 4 H, *CH*, ar), 7.37 (dt, ^3J = 7.6 Hz, *J* = 1.0 Hz, 4 H, *CH*, ar), 6.09 (d, ^1J = 473 Hz, 2 H, P*H*), 2.63-2.54 (m, 4 H, Flu-CH_2), 2.28-2.16 (m, 4 H, Cy-C*H*), 1.78-1.56 (m, 16 H, Cy-CH_2), 1.47-1.38 (m, 4 H, Cy-CH_2), 1.29-0.95 (m, 20 H, Cy-CH_2), 0.15-0.07 (m, 2 H, CH_2 (propyl)); $^{13}C\{^1H\}$ NMR (125.8 MHz, $CDCl_3$) δ 141.1 (d, *J(P,C)* = 4.3 Hz), 139.3 (d, *J(P,C)* = 3.3 Hz), 130.1, 129.1, 125.3, (d, *J(P,C)* = 2.8 Hz), 121.0, 51.9 (d, *J(P,C)* = 32.9 Hz), 32.3, 31.1, 30.9, 29.6 (d, *J(P,C)* = 3.2 Hz), 28.1 (d, *J(P,C)* = 3.2 Hz), 26.6 (d, *J(P,C)* = 13.0 Hz), 26.3 (d, *J(P,C)* = 12.7 Hz), 24.9; $^{31}P\{^1H\}$ NMR (121.4 MHz, $CDCl_3$) δ 37.3; ^{31}P NMR (121.4 MHz, $CDCl_3$) δ 37.3 (d, *J(P,H)* = 473 Hz); MS (70 eV) m/z 765.6 $[M\text{-}H^+]^+$, 568.3 $[M\text{-}PHCy_2]^+$.

1,4-Bis-(9-(dicyclohexylphosphinotetrafluoroborate)-fluorenyl)-butane (5b): 1,4-Difluorenylbutane **(5a)** (2.58 g, 6.68 mmol); *n*BuLi (5.34 mL, 13.4 mmol); Cy_2PCl (3.11 g,

13.4 mmol) afforded **5b** (5.64 g, 88 %) as a white powder. mp 262.0 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99-7.94 (m, 4 H, *CH*, ar), 7.78-7.74 (m, 4 H, *CH*, ar), 7.50-7.46 (m, 8 H, C*H*, ar), 6.29 (d, ^{1}J = 472 Hz, 2 H, P*H*), 2.88-2.82 (m, 4 H, Flu-CH_2), 2.53-2.42 (m, 4 H, PC*H*), 1.96-1.89 (m, 4 H, Cy-CH_2), 1.79-1.71 (m, 4 H, Cy-CH_2), 1.69-1.62 (m, 8 H, Cy-CH_2), 1.58-1.51 (m, 4 H, Cy-CH_2), 1.40-1.20 (m, 12 H, Cy-CH_2), 1.12-1.01 (m, 8 H, Cy-CH_2), 0.51-0.46 (m, 4H, CH_2 (butyl)); ^{13}C{^{1}H} NMR (125.8 MHz, $CDCl_3$) δ 141.7 (d, *J(P,C)* = 4.7 Hz), 140.3 (d, *J(P,C)* = 2.7 Hz), 130.3, 129.5, 126.1, (d, *J(P,C)* = 2.8 Hz), 121.0, 52.4 (d, *J(P,C)* = 33.3 Hz), 31.5 (d, *J(P,C)* = 8.7 Hz), 31.2, 30.1 (d, *J(P,C)* = 3.3 Hz), 28.7 (d, *J(P,C)* = 3.3 Hz), 27.0 (d, *J(P,C)* = 13.2 Hz), 26.6 (d, *J(P,C)* = 12.4 Hz), 25.5, 21.2 (d, *J(P,C)* = 11.2 Hz); ^{31}P{^{1}H} NMR (202.5 MHz, $CDCl_3$) δ 37.2; ^{31}P NMR (202.5 MHz, $CDCl_3$) δ 37.2 (d, *J(P,H)* = 471 Hz); MS (70 eV) m/z 779.6 [M-H$^+$]$^+$, 795.6 [MO-H$^+$]$^+$, 597.5 [MO-PHCy$_2$-H$^+$]$^+$.

1,5-Bis-(9-(dicyclohexylphosphinotetrafluoroborate)-fluorenyl)-pentane (6b): 1,5-Difluorenylpentane **(6a)** (2.40 g, 6.00 mmol); *n*BuLi (4.80 mL, 12.0 mmol); Cy_2PCl (2.78 g, 12.0 mmol) afforded **6b** (4.63 g, 80 %) as a white powder. mp 165.1-170.3 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (d, ^{3}J = 7.0 Hz, 4 H, *CH*, ar), 7.81 (dd, ^{3}J = 7.0 Hz, *J* = 1.6 Hz, 4 H, *CH*, ar), 7.54-7.47 (m, 8 H, *CH*, ar), 6.43 (d, ^{1}J = 475 Hz, 2 H, P*H*), 2.75-2.64 (m, 4 H, Flu-CH_2), 2.43-2.31 (m, 4 H, Cy-C*H*), 1.93-1.85 (m, 4 H, Cy-CH_2), 1.76-1.69 (m, 4 H, Cy-CH_2), 1.69-1.60 (m, 8 H, Cy-CH_2), 1.56-1.48 (m, 4 H, Cy-CH_2), 1.35-1.26 (m, 8 H, Cy-CH_2), 1.23-1.01 (m, 14 H, Cy-CH_2 and Flu-CH_2CH_2CH_2), 0.57-0.48 (m, 4 H, CH_2 (pentyl)); ^{13}C{^{1}H} NMR (125.8 MHz, $CDCl_3$) δ 141.3 (d, *J(P,C)* = 4.6 Hz), 140.2 (d, *J(P,C)* = 2.6 Hz), 130.1, 129.2, 125.5, (d, *J(P,C)* = 3.1 Hz), 120.8, 52.2 (d, *J(P,C)* = 33.1 Hz), 33.6, 31.1, 30.8, 29.6 (d, *J(P,C)* = 3.3 Hz), 28.2 (d, *J(P,C)* = 3.7 Hz), 26.6 (d, *J(P,C)* = 13.1 Hz), 26.3 (d, *J(P,C)* = 12.6 Hz), 25.0, 22.1 (d, *J(P,C)* = 9.8 Hz); ^{31}P{^{1}H} NMR (121.4 MHz, $CDCl_3$) δ 34.6; ^{31}P NMR (121.4 MHz, $CDCl_3$) δ 34.6 (d, *J(P,H)* = 475 Hz); MS (70 eV) m/z 793.6 [M-H$^+$]$^+$, 809.6 [MO-H$^+$]$^+$, 596.5 [M-PHCy$_2$-H$^+$]$^+$.

α,α'-Bis-(9-(dicyclohexylphosphinotetrafluoroborate)-fluorenyl)-*o*-xylene (7b): α,α'-Difluoren-9-yl-*o*-xylene **(7a)** (3.02 g, 6.90 mmol); *n*BuLi (5.53 mL, 13.8 mmol); Cy_2PCl (3.21 g, 13.8 mmol) afforded **7b** (5.5 g, 79 %) as a white powder. mp 250.4 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (d, ^{3}J = 7.0 Hz, 4 H, *CH*, ar), 7.67-7.64 (m, 4 H, *CH*, ar), 7.51-7.45 (m, 8 H, *CH*, ar), 6.65 (d, ^{1}J = 474 Hz, 2 H, P*H*), 6.12-6.07 (m, 2 H, *CH*, ar), 5.64-5.58 (m, 2 H, *CH*, ar), 4.13 (d, $^{3}J(P,H)$ = 7.4 Hz, 4 H, Flu$CH_{2benzyl}$), 2.44-2.32 (m, 4 H, Cy-C*H*), 2.10-2.02 (m, 4 H, Cy-CH_2), 1.85-1.77 (m, 4 H, Cy-CH_2), 1.73-1.63 (m, 8 H, Cy-CH_2), 1.61-1.45 (m, 8 H, Cy-CH_2), 1.41-1.30 (m, 4 H, Cy-CH_2), 1.29-1.09 (m, 12 H, Cy-CH_2); ^{13}C{^{1}H} NMR (125.8 MHz, $CDCl_3$) δ 141.3 (d, *J(P,C)* = 5.0 Hz), 139.5 (d, *J(P,C)* = 3.5 Hz), 131.7 (d, *J(P,C)* = 13.6 Hz), 130.3, (d, *J(P,C)* = 1.8 Hz), 129.0, (d, *J(P,C)* = 1.8 Hz), 128.1, 125.7 (d, *J(P,C)* = 3.3 Hz), 125.6, 121.0, 53.4 (d, *J(P,C)* = 32.0 Hz), 34.8 (d, *J(P,C)* = 2.2 Hz), 31.2 (d, *J(P,C)* = 34.4 Hz), 29.9 (d, *J(P,C)* = 3.4 Hz), 28.1 (d, *J(P,C)* = 3.1 Hz), 26.7 (d, *J(P,C)* = 12.8 Hz), 26.2 (d, *J(P,C)* = 12.7 Hz), 25.0; ^{31}P{^{1}H} NMR (202.5 MHz, $CDCl_3$) δ 36.9; ^{31}P NMR

(202.5 MHz, $CDCl_3$) δ 36.9 (d, *J(P,H)* = 474 Hz); MS (70 eV) m/z 827.7 $[M\text{-}H^+]^+$, 630.5 $[M\text{-}PHCy_2]^+$.

α,α'-Bis-(9-(dicyclohexylphosphinotetrafluoroborate)-fluorenyl)-*p*-xylene (8b): α,α'-Difluoren-9-yl-*p*-xylene **(8a)** (1.5 g, 3.45 mmol); *n*BuLi (2.76 mL, 6.90 mmol); Cy_2PCl (1.60 g, 6.90 mmol) afforded **8b** (3.3 g, 95 %) as a white powder. mp 256.8 °C; ^1H NMR (500 MHz, CD_3CN) δ 7.78 (d, ^3J = 7.6 Hz, 4 H, *CH*, ar), 7.71 (d, ^3J = 7.6 Hz, 4 H, *CH*, ar), 7.53 (t, ^3J = 7.6 Hz, 4 H, *CH*, ar), 7.41 (dt, ^3J = 7.6 Hz, *J* = 1.0 Hz, 4 H, *CH*, ar), 6.05 (d, ^1J = 463 Hz, 2 H, P*H*), 6.00 (s, 4 H, CH_{benzyl}, ar), 3.67 (d, $^3J(P,H)$ = 6.5 Hz, 4 H, Flu$CH_{2benzyl}$), 2.48-2.38 (m, 4 H, Cy-C*H*), 1.72-1.46 (m, 22 H, Cy-CH_2), 1.24-0.98 (m, 22 H, Cy-CH_2); $^{13}C\{^1H\}$ NMR (125.8 MHz, CD_3CN) δ 142.0 (d, *J(P,C)* = 5.0 Hz), 139.5 (d, *J(P,C)* = 3.0 Hz), 131.7 (d, *J(P,C)* = 13.9 Hz), 130.9, (d, *J(P,C)* = 1.8 Hz), 129.7, 128.8, (d, *J(P,C)* = 1.8 Hz), 126.5, (d, *J(P,C)* = 3.3 Hz), 122.0, 53.2 (d, *J(P,C)* = 32.3 Hz), 39.0, 31.6 (d, *J(P,C)* = 34.2 Hz), 29.7 (d, *J(P,C)* = 3.4 Hz), 28.7 (d, *J(P,C)* = 3.9 Hz), 26.9 (d, *J(P,C)* = 13.4 Hz), 26.7 (d, *J(P,C)* = 12.7 Hz), 25.2; $^{31}P\{^1H\}$ NMR (121.4 MHz, CD_3CN) δ 37.4; ^{31}P NMR (121.4 MHz, CD_3CN) δ 37.4 (d, *J(P,H)* = 464 Hz); MS (70 eV) m/z 827.7 $[M\text{-}H^+]^+$, 630.5 $[M\text{-}PHCy_2]^+$.

General cross coupling screening protocols

Buchwald–Hartwig amination of aryl halides with 3,5-dimethylaniline: The aryl halide (1 mmol), amine (1.5 mmol), NaO*t*Bu (2 mmol), $Pd(OAc)_2$ (1.12 mg, 0.005 mmol, 0.5 mol %) and the respective ligand (**2b**-**8b**) (0.01 mmol, 1 mol %) and dry toluene (5 mL) were placed in a Schlenk tube under an Ar-atmosphere. Heptadecane (200 µL) was added as an internal standard and the reaction mixture was stirred at 120 °C for 12 h in an Al-block. After cooling to RT, the reaction mixture was analyzed via GC. For the isolation of the amination product the reaction mixture was diluted with diethyl ether (15 mL) and washed with water (10 mL). Then the organic phase was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The product was purified by column chromatography (silica gel, cyclohexane / ethyl acetate / NEt_3 9:1:1) to afford (3,5-dimethyl-phenyl)-*p*-tolyl-amine as colorless needles.

Suzuki coupling of p-chloroacetophenone with tolylboronic acid:

(a) Preparation of the catalyst stock solution: $[Na_2PdCl_4]$(0.025 mmol), the respective ligand (**2b**-**8b**) (0.05 mmol) and Cs_2CO_3 (66 mg, 0.2 mmol) were placed in a Schlenk tube and evacuated and backfilled with argon thrice. Dioxane (5.0 mL) was added and the mixture was stirred at 60 °C for 2 h until the solution turned off white. This stock solution has a concentration of 0.005 mol% mL^{-1}·mmol aryl halide.

(b) Cross-coupling reaction: *p*-Tolylboronic acid (204 mg, 1.5 mmol) and Cs_2CO_3 (652 mg, 2.0 mmol) were placed in a 25 mL Schlenk-tube and evacuated and backfilled with argon thrice. Dioxane (5 mL), *p*-chloroacetophenone (129.8 µL, 1 mmol) and the respective volume of the catalyst stock solution (1 mL catalyst stock solution effects a cat.-loading of 0.5 mol% per mmol arylchloride) and heptadecane (200 µL) as an internal standard were added and the

reaction mixture was stirred for 15 h at 80 °C in an Al-block. After cooling to RT, the reaction mixture was analyzed via GC. For isolation of the coupling product the reaction mixture was diluted with diethyl ether (15 mL) and washed with water (10 mL). Then the organic phase was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The product was purified by column chromatography (silica gel, cyclohexane / ethyl acetate / 9:1) to afford 1-(4'-methyl-biphenyl-4-yl)-ethanone as white crystals.

Sonogashira reaction of 4-bromotoluene with phenylacetylene: Dry HN*i*Pr$_2$ (10 mL), *4*-bromotoluene (1.71 g, 1.22 mL, 10 mmol), and phenylacetylene (1.12 g, 1.21 mL, 11 mmol) were placed in a Schlenk tube and deaerated twice via freeze and thaw technique. Then the catalyst (0.00667 mol% Pd) was added in the given concentration as a ready-made mixture of [Na_2PdCl_4]/ligand (phosphonium salt)/CuI: (4:4:3) or (4:8:3), respectively, under argon. The reaction mixture was stirred for 24 h at 50 °C in an Al-block. After cooling to RT, the reaction mixture was analyzed via GC, quantitative analysis was performed via external calibration by calculating the response factors of pure samples of starting material (4-bromotoluene) and product. For isolation of the coupling product the reaction mixture was diluted with diethyl ether (15 mL) and washed with water (2 x 10 mL), then the organic phase was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The product was isolated by column chromatography (silica gel, cyclohexane/ethyl acetate 100:2) to afford 1-methyl-4-phenylethynyl-benzene as white crystals.

(3,5-Dimethyl-phenyl)-*p*-tolyl-amine: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.12 (d, ^3J = 8.2 Hz, 2 H, C*H*, ar), 7.03 (d, ^3J = 8.2 Hz, 2 H, C*H*, ar), 6.69 (s, 2 H, C*H*, ar), 6.59 (s, 1 H, C*H*, ar), 5.53 (s (br), 1 H, N*H*), 2.35 (s, 3 H, CH_3), 2.30 (s, 6 H, CH_3); ^{13}C{^{1}H} NMR (125.77 MHz, $CDCl_3$) δ 144.0, 140.6, 139.0, 130.8, 129.9, 122.3, 119.1, 114.8, 21.5, 20.7; ^{15}N NMR (50.69 MHz, $CDCl_3$) δ -294.6; elemental analysis calcd (%) for $C_{15}H_{17}N$: C 85.26, H 8.11, N 6.63; found: C 84.89, H 8.08, N 6.64; HRMS calcd. for $C_{15}H_{17}N$: 211.1361, found 211.13511.

1-(4'-Methyl-biphenyl-4-yl)-ethanone: mp 121.3 °C;^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (d, ^3J = 8.5 Hz, 2 H, C*H*, ar), 7.66 (d, ^3J = 8.5 Hz, 2 H, C*H*, ar), 7.52 (d, ^3J = 8.2 Hz, 2 H, C*H*, ar),7.27 (d, ^3J = 8.2 Hz, 2 H, C*H*, ar), 2.62 (s, 3 H, (CO)CH_3), 2.40 (s, 3 H, CH_3); ^{13}C{^{1}H} NMR (125.77 MHz, $CDCl_3$) δ 197.7, 145.7, 138.2, 137.0, 135.6, 129.7, 128.9, 127.1, 127.0, 26.6, 21.2; elemental analysis calcd (%) for $C_{15}H_{14}O$: C 85.68, H 6.71; found: C 85.60, H 6.74; HRMS calcd. for $C_{18}H_{14}N_2$: 210.1044, found 210.10444. The ^{1}H- and ^{13}C NMR spectra were identical to those in the literature.[123]

1-Methyl-4-phenylethynyl-benzene: mp 79.1 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (dd, ^3J = 7.8 Hz, J = 1.9 Hz, 2 H, C*H*, ar), 7.42 (d, ^3J = 8.0 Hz, 2 H, C*H*, ar), 7.35-7.29 (m, 3 H, C*H*, ar), 7.15 (dd, ^3J = 8.0 Hz, J = 0.6 Hz, 2 H, C*H*, ar), 2.36 (s, 3 H, CH_3); ^{13}C{^{1}H} NMR (125.77 MHz, $CDCl_3$) δ 138.8, 132.0, 131.9, 129.5, 128.7, 128.5, 123.9, 120.6, 90.0, 89.1, 21.9; elemental analysis calcd (%) for $C_{15}H_{12}$: C 93.71, H 6.29; found: C 93.58, H 6.28; HRMS

calcd. for $C_{15}H_{12}$: 192.0939, found 192.09198. The ^{1}H- and ^{13}C NMR spectra were identical to those in the literature.[124]

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4.9. Sulfonierte N-Heterocyclische Carbene für Suzuki-Reaktionen in Wasser als Reaktionsmedium

Der Inhalt dieses Kapitels wurde bereits veröffentlicht:

Christoph A. Fleckenstein, Sutapa Roy, Steffen Leuthäußer, Herbert Plenio, *"Sulfonated N-Heterocyclic Carbenes for Suzuki Coupling in Water", Chem. Comm.* **2007**, *27*, 2870-2872.

Neben Phosphinen etablierten sich auch *N*-Heterocyclische Carbene (*N*HCs) in den letzten Jahren als Liganden in palladiumvermittelten Kreuzkupplungen. Für Buchwald-Hartwig-Aminierungen sowie Suzuki-Kreuzkupplungen konnten von *Nolan et al.* Pd/*N*HC-Komplexe mit außerordentlich hoher Aktivität entwickelt werden, die auch in größerem Maßstab zur Verfügung stehen. Interessanterweise sind bislang nur wenige Kreuzkupplungsprotokolle von Pd/*N*HC-Komplexen in Verbindung mit Wasser oder wässrigen Reaktionsmedien bekannt. Ebenso wurde bis dato nur von wenigen gut wasserlöslichen *N*HCs in der Literatur berichtet. Aufgrund der ungenügenden Löslichkeit der Palladiumkomplexe mit bekannten *N*HCs erlaubt die Verwendung von reinem Wasser als Lösemittel bislang nicht den Einsatz von Chloraromaten auf breiter Linie. Eine dem als hochwasserlöslich bekannten Phosphinliganden Triphenylphosphintrisulfonat (TPPTS) analoge Modifikation eines *N*HC durch Derivatisierung mit Sulfonatogruppen (Abb. 69), die hochwasserlösliche *N*HC- bzw. Metallkomplexe verspricht, war bis dato nicht bekannt.

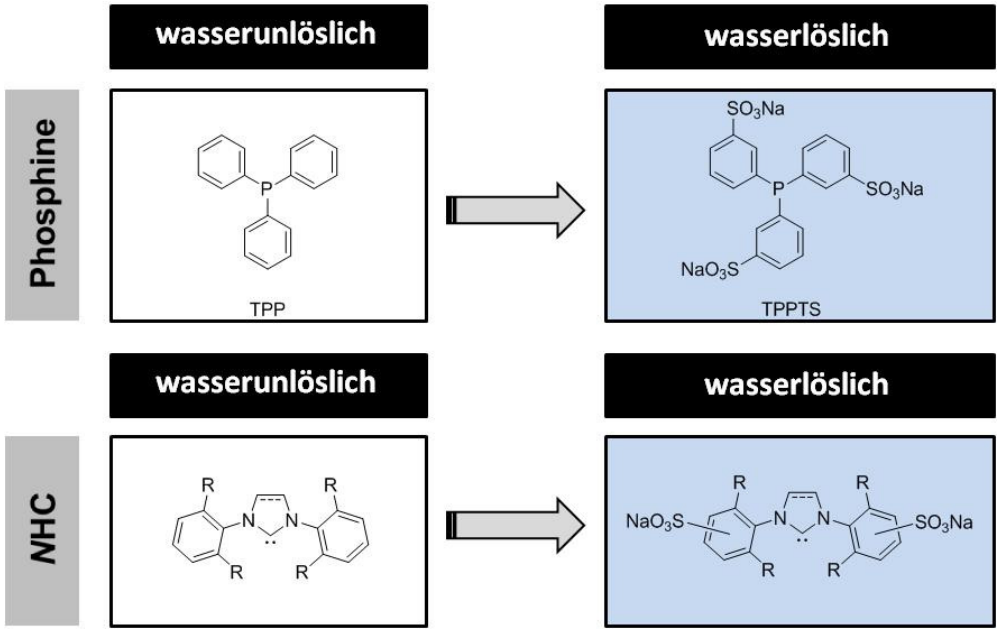
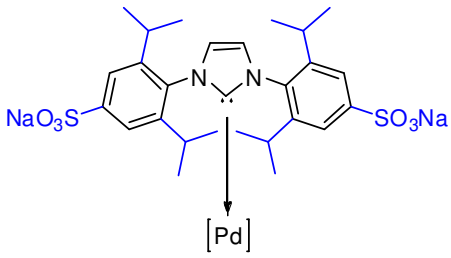


Abbildung 69. Hydrophilisierung durch Einführung von Sulfonatogruppen.

Im vorliegenden Kapitel wird die Synthese sechs sulfonierter *N*-Heterocyclischer Carbenliganden mit gesättigtem bzw. ungesättigtem Rückgrat beschrieben. Die Darstellung erfolgte durch Kondensation der entsprechend sulfonierten Anilinderivate mit Glyoxal. Ringschluss der resultierenden Diimine mit Pivalinsäurechlormethylester ergab die entsprechenden Imidazoliumsalze als Precursor der ungesättigten Carbene. Die Imidazoliniumsalze, Precursor der gesättigten Carbene, sind via Reduktion der Diimine und anschließendem Ringschluss mit Ameisensäureorthoethylester zugänglich.



Die *in situ* gebildeten Pd/*N*HC-Komplexe wurden erfolgreich als Katalysatoren in Suzuki-Kreuzkupplungsreaktionen in reinem Wasser als Lösemittel eingesetzt und auf ihre Aktivität hin getestet. Palladiumkomplexe mit sterisch anspruchsvollen, ungesättigten *N*HCs (siehe rechts) zeigten sich unter den gewählten Bedingungen als die aktivsten Katalysatoren. Die Kupplung verschiedener Chloraromaten gelang quantitativ mit 0.1 mol% dieser Pd-Komplexe. Problematische Substrate wie beispielsweise *p*-Chloranilin oder 4-Amino-2-chlorpyridin ließen sich mit 0.5 mol% des Katalysators kreuzkuppeln.

Die beobachtete katalytische Aktivität der wasserlöslichen Pd-Komplexe in Suzuki-Reaktionen mit *N*-Heterocyclen oder Substraten mit freien Aminofunktionalitäten ist ähnlich den besten literaturbekannten Katalysatoraktivitäten von *Buchwald et al.*, *Fu et al.* oder *Guram et al.* Das entwickelte Reaktionsprotokoll ist signifikant nachhaltiger als literaturbekannte Verfahren, da es auf Cosolventien wie Acetonitril oder Toluol verzichtet. Die sulfonierten *N*HCs sind somit sehr aktive Liganden mit interessantem Potential in Anwendungen in diversen Kreuzkupplungsreaktionen. Die Aktivität der wasserlöslichen Pd/*N*HC-Komplexe ist allerdings um mindestens den Faktor 10 geringer als die des von uns entwickelten, auf sulfonierten Fluorenylphosphinen basierenden Pd-*cataCXium®* *FSulf*-Systems. Somit ist Pd-*cataCXium®* *FSulf* sowohl aus Aktivitätsgründen als auch aufgrund besserer synthetischer Zugänglichkeit als das System der Wahl bei Suzuki-Reaktionen mit Heterocyclen anzusehen.

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Sulfonated N-heterocyclic carbenes for Suzuki coupling in water†

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Sulfonated, water-soluble imidazolium and imidazolinium salts were synthesized and the respective Pd-complexes with *N*,*N*′-bis(2,6-dialkyl-4-SO_3 -phenyl)imidazol-2-ylidene and *N*,*N*′-bis(2,6-dialkyl-4-SO_3 -phenyl)-4,5-dihydroimidazol-2-ylidene ligands were applied in aqueous Suzuki coupling reactions of aryl chlorides.

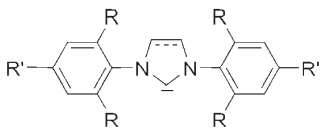
From an environmental as well as from an economic point of view, the use of volatile organic compounds as solvents for chemical transformations is under critical discussion and alternatives such as $scCO_2$,[1,2] ionic liquids[3] or water[4] are actively studied.[5]

Water especially as a cheap and non-toxic solvent has been receiving special attention[6] since the Ruhrchemie/Rhone-Poulenc hydroformylation process is carried out in an aqueous organic solvent mixture,[7] facilitating the recovery of the valuable rhodium catalyst. The need to replace organic solvents by water is more important in the fine chemicals industry since a much larger amount of waste per mass unit of product is generated[8]—of which the majority are solvents.[9]

Obviously catalytic reactions in water require water-soluble catalysts and it is a typical strategy to modify transition metal complexes by attaching phase tags which infer the desired solubility properties.[10,11] The most prominent solubilizing group in this respect is the sulfonato group; consequently, TPPTS [tri(*m*-sulfonyl)triphenylphosphine: triphenylphosphine, trisulfonated] is the most important ligand among numerous other water-soluble phosphines.[12–16]

Primarily due to their unique electron-donating abilities and the stability of the resulting metal complexes, N-heterocyclic carbenes are beginning to replace phosphines in a number of catalytic processes.[17–22] The most important class of NHC-ligands for catalytic applications is depicted in Scheme 1.

Two of the most important transition-metal catalyzed reactions, the Ru-mediated olefin metathesis and the large group of Pd-mediated cross-coupling reactions, rely on this class of NHC-ligands, as exemplified by the work of Grubbs[23] and Nolan *et al.*[17,24]



Scheme 1 R = Me or *i*Pr, saturated or unsaturated ring.

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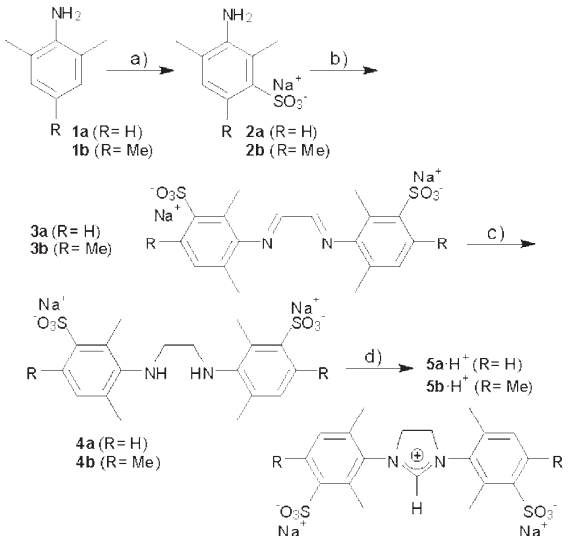
† Electronic supplementary information (ESI) available: Full experimental details and characterization of new compounds. See DOI: 10.1039/b703658b

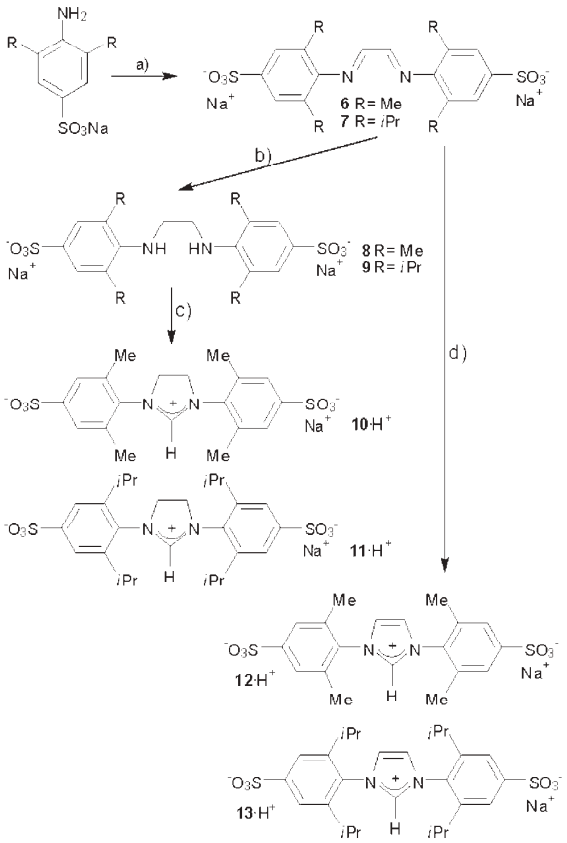
It is therefore surprising that to the best of our knowledge NHC-based relatives of TPPTS have not been described in the literature. A few hydrophilic NHC compounds are known[25,26] and have been used for cross-coupling reactions.[27,28] Recently, Grubbs utilized a PEG-decorated NHC for aqueous olefin metathesis.[29,30]

We wish to present here the synthesis of disulfonated N-heterocyclic imidazolium and imidazolinium salts (Schemes 2 and 3).‡ Starting from 2,6-dimethyl-3-(sulfonato-Na^+)aniline, which was prepared according to a procedure by Courtin *et al.*,[31] the condensation with glyoxal under carefully controlled reaction conditions generates the diimine **3a** in 72% yield. It should be noted here that in our hands the synthesis of **2a** is not reliable; since often a mixture of mono- and disulfonated aniline is formed. Fortunately, these problems can be avoided by applying the same sulfonation reaction conditions to 2,4,6-trimethylaniline, resulting in the monosulfonated aniline **2b**. Diimines **3** can be reduced under hydrogen pressure to generate the diamines **4**, which were cyclized to give the respective disulfonated imidazolinium salts **5**·H^+.

For the synthesis of the 4-sulfonato-substituted NHC-ligands a related approach was chosen. However, the formation of the respective diimines **6** and **7** is difficult when using a 40% aq. solution of glyoxal. The diimines are formed in good yields (>75%), but invariably contain a significant amount (>15%) of



Scheme 2 *Reagents and methods*: (a) 20% oleum; (b) ethanol, glyoxal, HCOOH; (c) MeOH, H_2, Pd/C; (d) EtOH, $HC(OEt)_3$, NH_4Cl, HCOOH.



Scheme 3 *Reagents and methods*: (a) Ethanol, 1,4-dioxane-2,3-diol, HCOOH; (b) MeOH, H_2, Pd/C; (c) EtOH, $HC(OEt)_3$, HCOOH; (d) chloromethyl pivalate, dmso.

unreacted aniline. Obviously, the equilibrium for the formation of the diimine and water is unfavourable. However, the diimine can be obtained in excellent yields when using 1,4-dioxane-2,3-diol, the anhydrous adduct of ethylene glycol and glyoxal. The Pd/C-catalyzed reduction of the pure diimines **6** and **7** in methanol with H_2 resulted in the formation of the desired diamines **8** and **9**. Again diamine **8** is contaminated with the respective aniline due to the facile hydrolysis of diimine **6**. This reduction proceeds cleanly only with strict exclusion of water. The cyclization of the diamines **8** and **9** to the respective imidazolinium salts, **10**·H^+ and **11**·H^+, utilizes $HC(OEt)_3$ according to standard procedures. The synthesis of the two imidazolium salts **12**·H^+ and **13**·H^+ was effected using chloromethyl pivalate as a C_1-building block.

In order to probe the catalytic performance of **5b** in Pd-mediated aqueous cross-coupling reactions,[32] we studied the Suzuki coupling of several aryl chlorides with a catalyst formed *in situ* from **5b**·H^+ and Na_2PdCl_4 in water with KOH as the base (Table 1). While the deprotonation of imidazolium or imidazolinium salts in protic solvents is not possible due to insufficient acidity,[33] the respective Pd–NHC complexes are directly obtained using palladium salts in the presence of base and the sulfonated carbene precursor **5b**·H^+ in pure water. The coupling procedure consists of mixing the respective NHC-precursor, Na_2PdCl_4 and KOH in water, stirring for 30 min to first allow for the formation

Table 1 Aqueous Suzuki coupling reaction of aryl chlorides utilizing azolium salts **5b**, **11** and **13**

Ar-Cl + Ar'-B(OH)$_2$ —(Na_2PdCl_4, NHC·H^+, 3 equiv. KOH, water, 100 °C, 12-16 h)→ Ar-Ar'

Entry	Aryl chloride	Boronic acid	Catalyst	NHC	Conv.[a]
1	4-Chlorotoluene	4-Tolyl	1 mol%	**5b**	>99%
2	4-Chloroanisole	4-Tolyl	1 mol%	**5b**	>99%
3	4-Chloroacetophenone	4-Tolyl	1 mol%	**5b**	>99%
4	4-Chlorobenzonitrile	4-Tolyl	1 mol%	**5b**	>99%
5	4-Chlorotoluene	4-Tolyl	0.5 mol%	**5b**	84%
6	4-Chloroacetophenone	4-Tolyl	1 mol%	**11**	63%
7	4-Chlorotoluene	4-Tolyl	1 mol%	**11**	56%
8	4-Chlorotoluene	4-Tolyl	1 mol%	**13**	>99%
9	4-Chlorotoluene	4-Tolyl	0.1 mol%	**13**	91%
10	4-Chloroacetophenone	4-Tolyl	0.1 mol%	**13**	>99%
11	4-Chlorobenzene-sulfonamide	4-Tolyl	0.1 mol%	**13**	>99%
12	4-Chloroanisole	4-Tolyl	0.1 mol%	**13**	74%
13	4-Chloroaniline	4-Tolyl	0.5 mol%	**13**	80%
14	2-Chloropyridine	4-Tolyl	0.1 mol%	**13**	>99%
15	2-Chloropyridine	1-Naphthyl	0.5 mol%	**13**	>99%
16	4-Amino-2-chloro-pyridine	1-Naphthyl	1 mol%	**13**	85%
17	2-Chloro-4-methyl-quinoline	1-Naphthyl	0.5 mol%	**13**	>99%

[a] Average of two runs.

of the NHC–Pd complex followed by addition of the substrates. A set of four aryl chlorides (Table 1, entries 1–4) was reacted with tolylboronic acid at 100 °C using 1 mol% of the Pd catalyst during 12 h to result in the near quantitative formation of the respective coupling products. However, when the Pd-catalyst concentration is lowered to 0.5 mol%, the limits of catalysts based on **5b** become apparent as only 84% of product is formed (entry 5).

*i*Pr-substituted NHC-ligands tend to be more active in cross-coupling reactions than their Me-substituted relatives. Consequently, we studied the imidazolinium salt **11**·H^+ and the imidazolium salt **13**·H^+ in Pd-catalyzed cross-coupling reactions. To our surprise, the saturated NHC-ligand **11** is less efficient than **5b**: even at 1 mol% catalyst loading the respective Pd complexes gave only 63% and 56% conversion with 4-chloroacetophenone and 4-chlorotoluene, respectively (entries 6 and 7). With ligand **11** the formation of a black Pd precipitate was observed during the first few minutes of the catalytic reaction, which is normally indicative of catalyst decomposition. Therefore we stopped screening this ligand. Fortunately, the Pd complex of **13** turned out to be a much more active catalyst. At 1 mol%, 4-chlorotoluene is converted in >99% yield and even at 0.1 mol% catalyst loading 91% of this coupling product is formed (entries 8 and 9). Activated aryl chlorides give full conversion at 0.1 mol% (entries 10 and 11), while the deactivated chloroaniline (entry 13) requires 0.5 mol% catalyst for an 80% conversion.

Remarkably, nitrogen-containing heterocycles are coupled with high efficiencies (entries 14–17). Not only 2-chloropyridine, but also difficult substrates such as 4-amino-2-chloropyridine or the related quinoline derivative are reacted in excellent yields with tolylboronic or naphthylboronic acid. These results compare favourably with catalysts published by Buchwald *et al.*,[32] Fu *et al.*,[34] and Guram *et al.*[35]

Consequently, even the first generation of water-soluble NHC–Pd complexes is comparable in activity to the phosphines described in the literature for aqueous Suzuki reactions.[16,36]

In conclusion, the successful synthesis of sulfonated imidazolium and imidazolinium salts opens the door to the aqueous organometallic chemistry of NHC-ligands. In a preliminary study we have demonstrated the utility of sulfonated NHC-ligands in the aqueous Suzuki coupling of aryl chlorides; additional optimization of the catalytic performance in water will be undertaken in the future.

Notes and references

‡ All NMR spectra were recorded in dmso-d_6 at 300 MHz (^{1}H NMR) and 75.5 MHz (^{13}C NMR).

2,6-Dimethyl-3-(sulfonato-Na$^+$)aniline (**2a**). ^{1}H-NMR: δ 2.06 (s, 3H, CH_3), 2.29 (s, 3H, CH_3), 4.45 (s, 2H, NH_2), 6.73 (d, 1H, ArH, J = 9 Hz), 7.01 (d, 1H, ArH, J = 9 Hz). ^{13}C-NMR: δ 14.2 (CH_3), 17.9 (CH_3), 115.0 (aryl-CH), 118.2 (aryl-CH), 121.9 (aryl-CMe), 125.6 (aryl-CMe), 144.1 (aryl-CSO_3Na), 144.5 (aryl-CNH_2).

N,N′-(Ethane-1,2-diylidene)-bis[2,6-dimethyl-3-(sulfonato-Na$^+$)]aniline (**3a**). In a round-bottom flask the sulfonated aniline **2a** (10.0 g, 44.8 mmol) was dissolved in methanol (2500 mL). Then glyoxal (4.1 mL, 22.4 mmol) was added dropwise to the solution, followed by the addition of two drops of formic acid. The reaction mixture was stirred overnight at room temperature and then for 24 h at 50 °C. A yellow solid precipitated which was filtered off and then dried *in vacuo*. Yield: 8.1 g (16.1 mmol, 72%). ^{1}H-NMR: δ 2.08 (s, 6H, CH_3), 2.32 (s, 6H, CH_3), 7.05 (d, 2H, CH, J_{H-H} = 9 Hz), 7.53 (d, 2H, CH, J_{H-H} = 9 Hz), 8.10 (s, 2H, CH). ^{13}C-NMR: δ 14.8 (CH_3), 18.0 (CH_3), 123.0 (HC_{aryl}), 123.9 (HC_{aryl}), 125.9 (C_{aryl}-Me), 126.4 (C_{aryl}-Me), 144.9 (C-SO_3Na), 150.2 (C_{aryl}-N), 163.9 (HC_{imine}). HR-MS calcd for $C_{18}H_{18}N_2NaO_6S_2$ (M − NaCl) 445.0504; found: 445.0509.

N,N′-Ethane-bis[2,6-dimethyl-3-(sulfonato-Na$^+$)]aniline (**4a**). 5.0 g (10.0 mmol) of the diimine **3a** was dissolved in methanol (120 mL) in an autoclave flask. Then Pd/C 10% (1.13 g, 1.2 mmol) was added to the solution and the mixture was stirred for 3 h under 7 bar H_2 pressure. The Pd/C was filtered off through celite and the solution was evaporated under reduced pressure to obtain the diamine as a white solid. Yield: 4.1 g (8.1 mmol, 84%). ^{1}H-NMR: δ 2.20 (s, 6H, CH_3), 2.43 (s, 6H, CH_3), 3.00 (s, 4H, CH_2), 6.86 (d, 2H, CH, J_{H-H} = 9 Hz), 7.32 (d, 2H, CH, J_{H-H} = 9 Hz). ^{13}C-NMR: δ 14.8 (CH_3), 18.5 (CH_3), 48.5 (H_2C_{amine}), 120.4 (HC_{aryl}), 126.3 (HC_{aryl}), 127.9 (C_{aryl}-Me), 130.8 (C_{aryl}-Me), 144.6 (C-SO_3Na), 146.8 (C_{aryl}-N). HR-MS calcd for $C_{18}H_{22}N_2NaO_6S_2$ (M − NaCl) 449.08173; found: 449.08208.

1,3-Bis[2,6-dimethyl-3-(sulfonato-Na$^+$)phenyl]imidazolinium chloride (**5a**). To a solution of the diamine (**4a**) (1.5 g, 3.0 mmol) in ethanol (30 mL), were added triethylorthoformate (20 mL), NH_4Cl (0.16 g, 3.0 mmol) and a single drop of formic acid. The reaction mixture was refluxed for 2 d. The precipitated solid was filtered, washed with ether and then dried under vacuum. Yield: 0.87 g (1.7 mmol, 52%). ^{1}H-NMR: δ 2.38 (s, 6H, CH_3), 2.61 (s, 6H, CH_3), 4.49 (s, 4H, CH), 7.23 (d, 2H, CH, J_{H-H} = 9 Hz), 7.83 (d, 2H, CH, J_{H-H} = 9 Hz), 9.11, 9.15 (Im-CH). ^{13}C-NMR: δ 14.6 (CH_3), 17.5 (CH_3), 50.9 (CH_2), 127.4 (HC_{aryl}), 128.1 (HC_{aryl}), 133.9 (C_{aryl}-Me), 136.3 (C_{aryl}-Me), 145.7 (C-SO_3Na), 145.9 (C_{aryl}-N), 160.5 (HC_{im}-N). HR-MS calcd for $C_{19}H_{21}N_2NaO_6S_2$ (M − NaCl) 483.06368; found: 483.06274.

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4.10. Randaktivitäten

4.10.1. Redox-schaltbare Phasenmarkierungen: Verfahrensverbesserungen bei Mitsunobu-Reaktionen durch ferrocenylmarkiertes Triphenylphosphin

Der Inhalt dieses Kapitels wurde bereits veröffentlicht:

Christoph A. Fleckenstein, Herbert Plenio, *"Redox-Switchable Phase Tags-Facile Mitsunobu Reactions using Ferrocenyl-Tagged Triphenylphosphine"*, *Adv. Synth. Catal.* **2006**, *348*, 1058-1062.

Die Mitsunobu-Reaktion ermöglicht die Kondensation von Alkoholen mit hinreichend aciden Pronucleophilen, typischerweise unter Verwendung von Reagenzien wie Triphenylphosphin (TPP) und Diethylazodicarboxylat (DEAD) (Abb. 70). Auf diese Weise gelingt die Synthese von Estern, Aryl-Alkyl-Ethern, Thioethern, Amiden und zahlreichen weiteren Produkten unter milden Bedingungen. Die Mitsunobu-Reaktion verläuft stereoselektiv unter Inversion am hydroxyltragenden Kohlenstoffatom. Dies macht die Mitsunobu-Reaktion interessant für die Synthese chiraler Verbindungen und Naturstoffe.

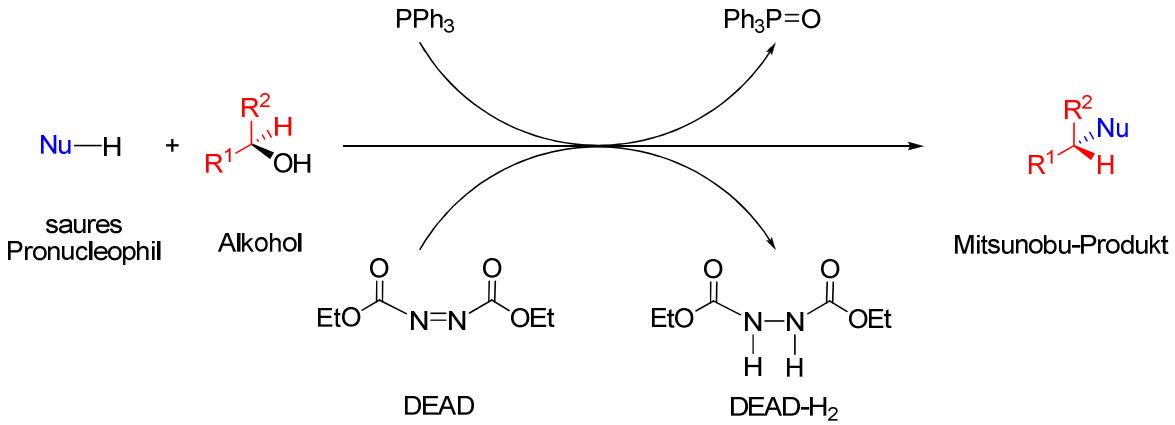

Abbildung 70. Allgemeines Schema der Mitsunobu-Reaktion.

Ein Problem bei der Mitsunobu-Reaktion stellt jedoch die stöchiometrische Verwendung von TPP und DEAD als Reagenzien dar, die im Anschluss an die Reaktion vom gewünschten Produkt abgetrennt werden müssen. Insbesondere das in der Reaktion aus TPP anfallende Triphenylphosphinoxid stellt eine schwer zu entfernende Verunreinigung

dar, deren Abtrennung oft einen chromatographischen Reinigungsschritt notwendig macht. Neuere Arbeiten beschäftigen sich vielfach mit der Problematik der Aufarbeitung von Mitsunobu-Reaktionen und der Separation des Produkts von TPPO. Zur Vereinfachung der Separation werden meist phasenmarkierte Triphenylphosphine als Reagenzien in Mitsunobu-Reaktionen eingesetzt. Bei den verwendeten Phasenmarkierungen lässt sich zwischen statischen (nicht schaltbaren) und dynamischen (schaltbaren) Markierungen unterscheiden. Zu den typischen statischen Phasenmarkierungen für Triphenylphosphine gehören:

- Trägerung auf Polymeren (Separation durch Filtration)
- Markierung mit permanent polaren Gruppen, z.B. Polyethylenglykol (Separation durch wässrige Extraktion)
- Fluorphasenmarkierung (Separation durch Festphasenextraktion, Chromatographie über Fluorphasen)

Eine dynamische Phasenmarkierung liegt beispielsweise bei der Verwendung von Diphenylpyridylphosphin vor, das durch Protonierung mit einer Brønsted-Säure nach Beendigung der Reaktion als entsprechendes Pyridyliumkation polar vorliegt und sich leicht wässrig entfernen lässt.

In diesem Kapitel werden Synthese und Anwendung von redoxschaltbarem, phasenmarkiertem Ferrocenyltriphenylphosphin beschrieben. Diese von *Plenio und Süßner* 2005 erstmals für Olefinmetathesekatalysatoren beschriebene Art der Phasenmarkierung vereinigt für den Einsatz in der Mitsunobu-Reaktion die Vorteile guter Aktivität sowie Orthogonalität zu vielen gängigen Schutzgruppen. Abbildung 71 beschreibt den Einsatz des ferrocenylmarkierten Triphenylphosphins in der Mitsunobu-Reaktion.

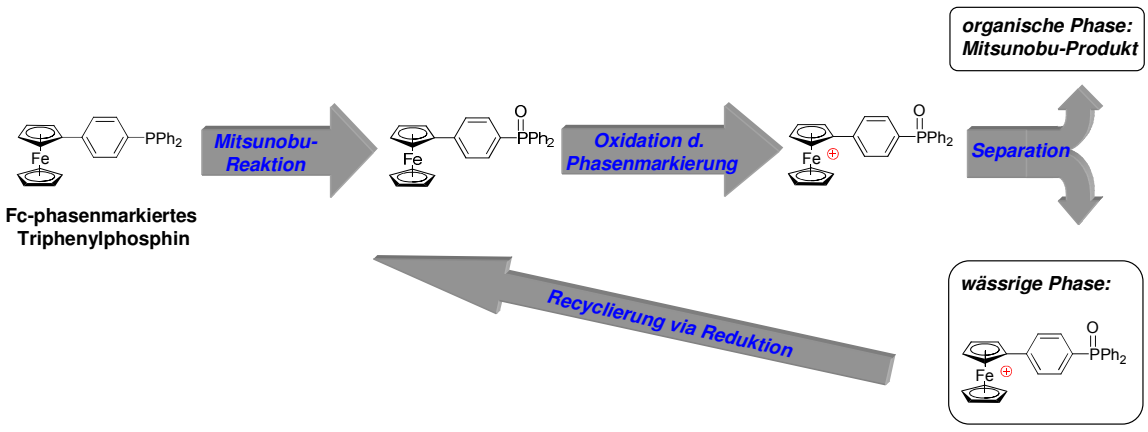

Abbildung 71. Erleichterung der Produktseparation in Mitsunobu-Reaktionen durch Einsatz von ferrocenyl-phasenmarkiertem Triphenylphosphin.

Die Umsetzbarkeit des in Abbildung 71 beschriebenen optimierten Mitsunobu-Reaktionsprotokolls konnte anhand von zwölf Testreaktionen (Synthese verschiedener Ester, Aryl-Alkylether und *N*-Alkylphthalimide) demonstriert werden.

Folgende Vorteile sind mit dem neuen Konzept verbunden:

- Reaktivität vergleichbar mit konventionellem TPP als Reagenz
- orthogonale Phasenschaltbarkeit des Ferrocens mit preiswertem, nichttoxischem Oxidationsmittel ($FeCl_3$)
- einfache wässrig/organische Produktseparation, hohe Produktausbeute (>90 %), hohe Reinheit des Rohprodukts
- Möglichkeit der Reduktion des markierten Triphenylphosphins (Triphenylphosphinoxids) mit $Na_2S_2O_3$ und $HSiCl_3$ und somit Recyclierung des Mitsunobu-Reagenzes

FULL PAPERS

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Redox-Switchable Phase Tags – Facile Mitsunobu Reactions using Ferrocenyl-Tagged Triphenylphosphine

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Abstract: The use of redox-switched phase tags in ferrocenyl-substituted triphenylphosphine combined with DBAD (di-*tert*-butyl azodicarboxylate) allows high yield (>90%) Mitsunobu transformations without the need for the chromatographic purification of the products. The redox-switchable phosphine can be easily synthesized in two steps from 4-bromoaniline, ferrocene and chlorodiphenylphosphine. It is separated from the reaction mixture by oxidation with iron(III) chloride and can be recycled efficiently by reductive treatment.

Keywords: ferrocene; Mitsunobu reaction; phosphanes; redox reaction; redox-switchable phase tag

Introduction

The implementation of efficient purification strategies in chemical synthesis is now considered to be an important issue for the applicability of chemical transformations. In this respect an enlightening contribution from Curran, reminded chemists that even in the presence of powerful (though time-consuming) separation techniques such as chromatography, both synthesis and separation determine the practical value of a reaction.[1]

However, there are a number of chemical transformations that are highly useful from a synthetic point of view, but are often plagued by purification problems. Infamous in this respect are reactions in which triphenylphosphine is used as a stoichiometric reagent[2] such as the Mitsunobu[3] and the Staudinger reactions[4] or the reduction of primary ozonides.[5]

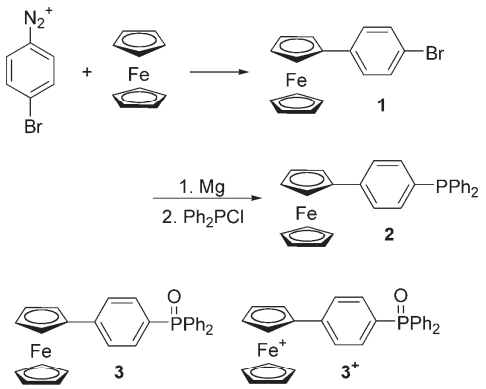
Nonetheless, the Mitsunobu reaction is a powerful synthetic tool for the condensation of an acidic pronucleophile (RXH) and an alcohol (R′OH), due to its wide applicability, stereospecificity and mild reaction conditions. Several strategies have been developed to deal with purification problems in the Mitsunobu reaction such as polymer-supported reagents,[6] basic phosphines,[7] tagged phosphines, various azodicarboxylate reagents,[8,9] fluorous reagents,[10] or phase switching approaches,[11] as described in detail in a recent review by Dandapani and Curran, dealing exclusively with Mitsunobu purification strategies.[12] Ideally such approaches yield pure products obviating chromatography, which is especially important for combinatorial library synthesis.

For the separation of organometallic catalyst complexes we have recently introduced redox-switchable phase tags, which are composed of ferrocenyl groups whose oxidation state can be changed reversibly.[13] In the reduced state such phase tags are neutral and as such are lipophilic units with a good solubility in non-polar solvents. However, on oxidizing the ferrocenyl groups with a mild oxidation reagent, the neutral phase tag is converted into a cationic group, which immediately precipitates from non-polar solvents. A significant advantage in the separation of reagents/catalysts with attached redox-active phase tags is the orthogonality of the solubility determining reductive or oxidative transformation of the phase tag. Furthermore, the redox potential of such phase tags can be adjusted easily to match different reaction conditions and substrates.

We now describe the synthesis and the redox-switched separation of ferrocenyl-tagged triphenylphosphine which is used as a stoichiometric reagent in the Mitsunobu reaction.

Results and Discussion

To be attractive for the user, the synthesis of a redox-switchable triphenylphosphine should be as simple as possible. We have thus devised a two-step procedure (Scheme 1) starting from relatively inexpensive,



Scheme 1. Synthesis of ferrocenyl-tagged PPh_3 (**2**).

commercially available materials such as ferrocene, 4-bromoaniline and diphenylchlorophosphine.

Following the diazotation of 4-bromoaniline, the reaction of the diazonium salt with ferrocene was performed under phase-transfer conditions,[14] to easily yield deca-gram amounts of 4-bromophenylferrocene (**1**) in 74% yield. Next, the Grignard reagent generated from **1** is reacted with diphenylchlorophosphine to result in the formation of the ferrocenyl-tagged triphenylphosphine (**2**) in 83% yield.

The redox potentials of the ferrocenes such as **1** ($E_{1/2}=0.491$ V; $\Delta E=78$ mV), **2** ($E_{1/2}=0.477$ V; $\Delta E=82$ mV) and **3** ($E_{1/2}=0.517$ V; $\Delta E=74$ mV) were determined by cyclic voltammetry (Figure 1).

The choice of the oxidation reagent used to switch the phase tag is critical for the usefulness of the redox-switchable phase tag approach described here. In principle, numerous oxidants are able to convert ferrocene into the respective ferrocene cation, however, the strength of the oxidizer needs to be adjusted to enable quantitative oxidation and to avoid over-oxidation, i.e., decomposition of the ferrocene cation.[15]

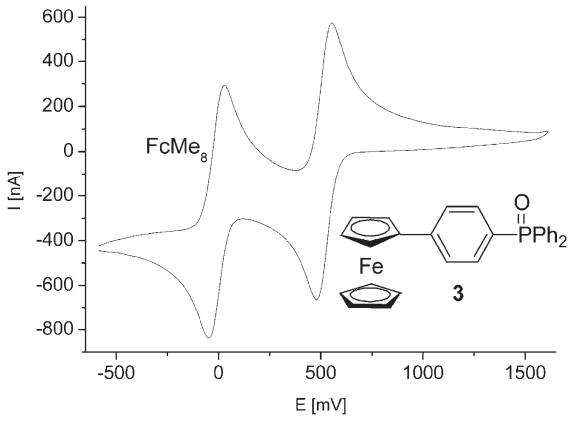


Figure 1. Cyclic voltammogram of **3**, referenced *vs.* $FcMe_8$.

Furthermore, when switching stoichiometric reagents such as **3**, a cheap, easily available and non-toxic oxidant would significantly enhance the impact of this approach. This oxidant should be soluble in the organic solvent used for the Mitsunobu reaction, to effect rapid oxidation of the phase tag.

With these limitations in mind, we decided to use anhydrous iron(III) chloride, which is cheap, readily available and soluble in THF. Most importantly, its oxidizing power is sufficient to quantitatively convert **2** and **3** into the corresponding ferrocenium salts. After the Mitsunobu reaction, solid iron(III) chloride or a solution in THF was added to the reaction mixture in the same solvent to oxidize the phase tag. The various iron salts can now be extracted with water. In this manner >98% of the ferrocenyl-tagged phosphine oxide $\mathbf{3}^+$ are removed. When using di-*tert*-butyl azodicarboxylate (DBAD) 4M HCl is next added to destroy the spent Mitsunobu reagent. This highly acidic approach may impose limits with respect to certain acid-labile substrates. However, the redox-switched separation described here is also compatible with other removal strategies which have been applied for modified DEAD (diethyl azodicarboxylate) or DIAD (diisopropyl azodicarboxylate).[12] It is also possible to attach redox-switchable phase tags to the azodicarboxylate by generating the respective ester of ferrocenylmethanol. However, this could lead to complications in the recovery of reagent **2**.

Following the Mitsunobu procedure listed in detail in the Experimental Section the respective products can be isolated in excellent yields (Table 1), with a high purity of the crude products not requiring chromatographic purification.

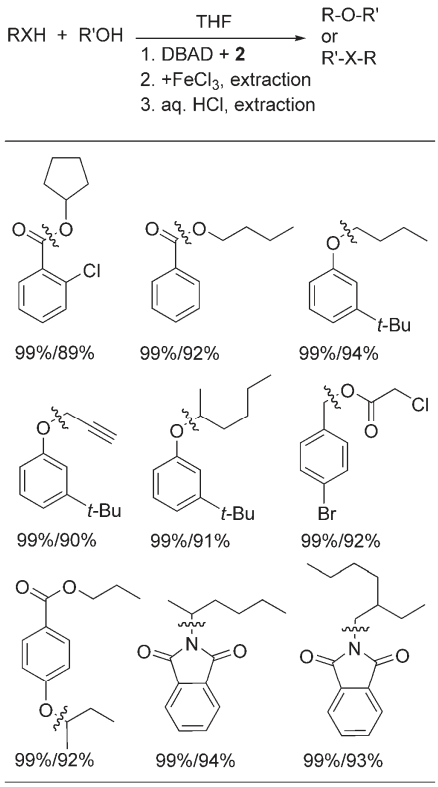
Furthermore, it is very easy to recover $\mathbf{3}^+$ from the aqueous phase by simply adding the reductant sodium thiosulfate which converts $\mathbf{3}^+$ to **3** (Scheme 2). Following the addition of THF and diethyl ether, ferrocene **3** can be re-extracted into the organic phase, from which it is isolated after evaporation. Reduction ($R_3PO \rightarrow R_3P$) of residual **3** with trichlorosilane allows the re-isolation of more than 80% of the initially added ferrocenylphosphine **2**.

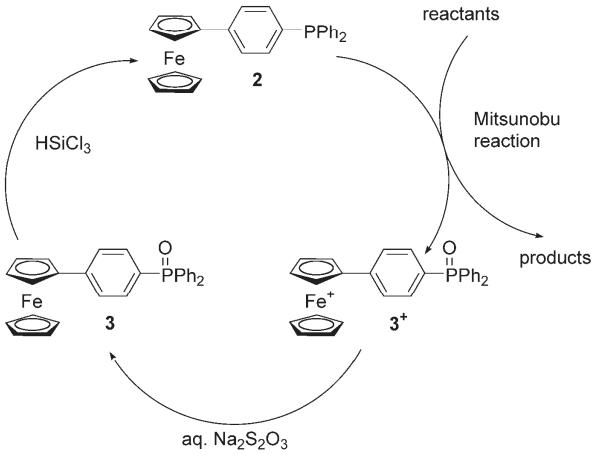
Finally, we were also interested whether the ferrocenyl-group has a significant influence on the Mitsunobu reactivity. Therefore we have monitored the conversion-time curve for the Mitsunobu reactions of chloroacetic acid and 2-propanol using the two different phosphines triphenylphosphine and **2**, which display roughly identical rates of product formation (Figure 2).

Conclusions

In conclusion, we have demonstrated that the use of redox-switchable phase tags allows us to reversibly

Table 1. General scheme of the Mitsunobu reaction and a list of the products synthesized (conversion/isolated yield), wavy lines denote the bonds formed.





Scheme 2. Recycling of ferrocenyl-tagged PPh_3.

modify the solubility properties of a substituted triphenylphosphine enabling the facile separation of the corresponding phosphine oxide. In combination with

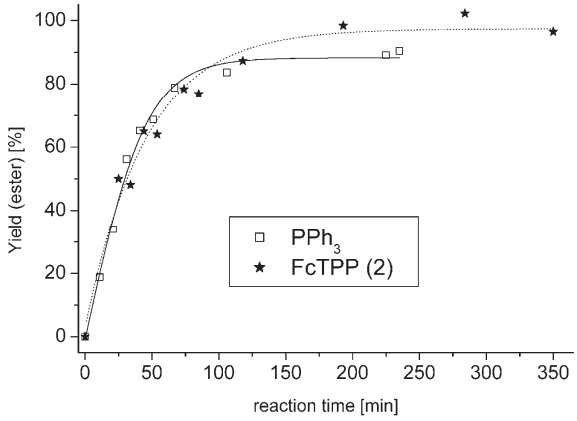


Figure 2. Comparison of reactivity for PPh_3 and the ferrocenyl-tagged PPh_3 (**2**); reaction temperature 0 °C; determination of yield *via* GC using isooctane as an internal standard.

DBAD, Mitsunobu products can be synthesized in typically > 90 % yields without the need for chromatographic purification.

Experimental Section

General Remarks

All chemicals were purchased as reagent grade from commercial suppliers and used without further purification, unless otherwise noted. THF was distilled over potassium and benzophenone under an argon atmosphere, Toluene was distilled over sodium and benzophenone under an argon atmosphere. Proton (^{1}H NMR), carbon (^{13}C NMR) and phosphorus (^{31}P NMR) nuclear magnetic resonance spectra were recorded on a Bruker DRX 500 at 500 MHz, 125.75 MHz and 202.46, respectively, and are referenced to tetramethylsilane ($\delta = 0.0$ ppm), for ^{1}H and ^{13}C NMR, and to H_3PO_4 ($\delta = 0.0$ ppm) for ^{31}P NMR. Thin layer chromatography: Fluka silica gel 60 F 254 (0.2 mm) on aluminum plates. Column chromatography: E. Merck silica gel 60 (0.063–0.20 mesh ASTM). Mass spectra (MS) were recorded on an Agilent 1100 HPLC-MS (column: YMC J'Sphere ODS H80, 4 μm, 20 × 2.1 mm; flow: 1.0 mL min^{-1}; $T = 30$ °C; eluent: (A: water + 0.05 % TFA/B: acetonitrile + 0.05 % TFA) 0.00 min: 4 % B → 2.00 min: 95 % B → 2.45 min: 4 % B); detection: UV + MS (ESI/quadrupole). GC experiments were run on a Perkin–Elmer AutoSystem, CP-Sil (CB, l = 15 m, $d_i = 0.25$ mm, $d_F = 1$ μm), N_2 (flow: 17 cm/sec; split 1:20), FID. Cyclic voltammetry: EG&G 263 A-2 potentiostat. All cyclic voltammograms were recorded in dry CH_2Cl_2 under an argon atmosphere at ambient temperature. A three-electrode configuration was employed. The working electrode was a Pt disk (diameter 1 mm) sealed in soft glass with a Pt wire as counterelectrode. The pseudoreference electrode was an Ag wire. Potentials were calibrated internally against the formal potential of octamethylferrocene

[10 mV (CH_2Cl_2) vs. Ag/AgCl]. NBu_4PF_6 (0.1 mol/L) was used as supporting electrolyte. *p*-Bromophenylferrocene was first prepared by Rosenblum et al.[16]

p-Bromophenylferrocene (1)

In a 1 L round-bottom flask 4-bromoaniline (52.5 g, 339 mmol) was suspended in 300 mL half-concentrated sulfuric acid. Within 30 min. 135 mL of an aqueous solution of $NaNO_2$ (2.5 mol/L) were added at 0°C. After stirring for an additional 30 min at 0°C and securing an excess of HNO_2 by use of KI-starch paper, the resulting clear yellow diazonium solution was added to a vigorously stirred solution of ferrocene (21.0 g, 113 mmol) in 600 mL Et_2O and Aliquat 336 (9 g) within 30 min. The reaction mixture was stirred vigorously for 1.5 h at 0°C and for 30 min at ambient temperature. The reaction mixture was transferred in a separation funnel and the aqueous phase was extracted with Et_2O (3×200 mL). The combined organic phases were washed subsequently with 200 mL water, then 200 mL brine and finally dried with $MgSO_4$. Filtration and concentration under vacuum gave the crude product which was dissolved in 25 mL ethyl acetate and adsorbed on silica gel. Column chromatography (silica, cyclohexane) afforded pure **1** (CAS 58482-65-8) as brown crystals; yield: 28.5 g (74%); R_f 0.44 (cyclohexane). ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.39 (d, ^3J=9.0 Hz, 2H, arom), 7.32 (d, ^3J=8.5 Hz, 2H, arom), 4.60 (t, J=2.0 Hz, 2H, Fc), 4.32 (t, J=2.0 Hz, 2H, Fc), 4.03 (s, 5H, Fc); ^{13}C{^{1}H} NMR (125.77 MHz, $CDCl_3$): δ=138.5, 131.4, 127.6, 119.4, 84.1, 69.7, 69.2, 66.4.

Diphenyl(*p*-ferrocenylphenyl)phosphine (FcTPP) (2)

Grignard route: In a 250 mL round-bottom flask Mg turnings (158 mg, 6.5 mmol) were placed under an argon atmosphere. *p*-Bromophenylferrocene (2.0 g, 5.9 mmol), dissolved in 80 mL dry THF, was added at ambient temperature and sonicated for 12 h. The Grignard solution was transferred into a 250 mL Schlenk-flask, containing Ph_2PCl (1.24 mL, 6.9 mmol), dissolved in dry THF (20 mL). The resulting reaction mixture was stirred for 4 h at ambient temperature. Silica gel (5 g) was added and volatiles were removed under vacuum. Purification *via* column chromatography (silica gel, 100:2 cyclohexane/EtOAc) afforded **2** as a red viscous oil; yield: 2.1 g (81%); R_f 0.60 (100:2 cyclohexane/EtOAc).

t-BuLi route: In a 100 mL Schlenk flask *p*-bromophenylferrocene (3.0 g, 8.8 mmol) was dissolved in 50 mL absolute THF. Under an argon-atmosphere *t*-BuLi, 1.5 M in pentane (6.0 mL, 8.9 mmol) was added at −78°C within 10 min. The now brownish solution was stirred for additional 2 h at that temperature before $PhPCl_2$ (1.75 mL, 2.15 g, 9.75 mmol) was added. The reaction mixture was stirred for 1 h at −78°C and further 2 h at ambient temperature. Silica gel (5 g) was added and volatiles were removed under vacuum. Purification *via* column chromatography (silica gel, 100:2 cyclohexane/EtOAc) afforded **2** as a red viscous oil; yield: 3.25 g (83%); R_f 0.60 (100:2 cyclohexane/EtOAc). ^{1}H NMR (acetone-d_6): δ=7.43–7.07 (m, 14H, arom), 4.62 (t, J=1.8 Hz, 2H, Fc), 4.21 (t, J=1.8, 2H, Fc), 3.88 (s, 5H, Fc); ^{13}C{^{1}H} NMR (acetone-d_6): δ=141.9, 139.0 (d, $J_{P,C}$=12.3 Hz), 138.9 (d, $J_{P,C}$=9.9 Hz), 134.9, 134.7, 130.1, 129.8 (d, $J_{P,C}$=11.9 Hz), 127.4 (d, $J_{P,C}$=6.8 Hz), 85.6, 70.8, 70.5, 67.8; ^{31}P NMR (acetone-d_6): δ=−7.81; anal. calcd. for $C_{28}H_{23}FeP$ (446.3): C 75.4, H 5.20; found: C 75.3, H 4.95.

General Mitsunobu Procedure

To a stirred solution of the nucleophile (carbonic acid or phenol or phthalimide) (1.3 mmol), FcTPP **2** (1.3 mmol) and the alcohol (1.0 mmol) in dry THF (3 mL), di-*tert*-butyl azodicarboxylate (1.3 mmol) dissolved in dry THF (2 mL) was added. The resulting solution was stirred overnight at ambient temperature. The reaction mixture was treated with $FeCl_3$ (500 mg) and stirred for 5 min, then Et_2O (10 mL) and water (10 mL) were added. The separated organic phase was treated again with $FeCl_3$ (200 mg), stirred for 5 min and washed with water. Then 5 mL HCl (4.0 mol/L in dioxane, 20 mmol) were added to the slightly yellow organic phase and stirred for 1 h. The solution was washed with water (2×20 mL), dried with $MgSO_4$ and filtered. Volatiles were removed under vacuum. The crude product was filtered through a pad of silica gel (5 cm, eluent: cyclohexane/ethyl acetate, 10:1). Volatile compounds of the filtrate were removed under vacuum, affording the respective products as slightly yellow oils (>90% isolated yield).

Cyclopentyl 2-chlorobenzoate (CAS 501356-76-9): ^{1}H NMR ($CDCl_3$): δ=7.77 (dd, ^3J=5 Hz, ^4J=1.5 Hz, 1H, *o*-C*H*, arom), 7.44–7.37 (m, 3H, C*H*, arom), 5.44 (m, 1H, COOC*H*), 1.97–1.64 (m, 8H, CH_2); ^{13}C{^{1}H} NMR (125.77 MHz, $CDCl_3$): δ=165.7, 133.4, 132.2, 131.2, 131.0, 130.9, 126.5, 78.6, 32.8, 23.8.

***n*-Butyl 3-*tert*-butylphenyl ether** (CAS 136-60-7): ^{1}H NMR ($CDCl_3$): δ=7.14 (t, ^3J=8 Hz, 1H, *m*-C*H*, arom), 6.90–6.86 (m, 2H, C*H*, arom), 6.65–6.62 (m, 1H, C*H*, arom), 3.89 (t, ^3J=6.5 Hz, 2H, O-CH_2), 1.73–1.67 (m, 2H, CH_2), 1.47–1.39 (m, 2H, CH_2), 1.24 (s, 9H, *t*-Bu), 0.91 (t, ^3J=8 Hz, 3H, CH_2CH_3); ^{13}C{^{1}H} NMR ($CDCl_3$): δ=158.0, 151.9, 127.9, 116.6, 111.6, 109.5, 66.5, 33.7, 30.5, 30.3, 18.3, 12.9; MS: m/z=207 $[M+H]^+$.

3-Prop-2-ynyl 3-*tert*-butylphenyl ether: ^{1}H NMR ($CDCl_3$): δ=7.16 (t, ^3J=7.5 Hz, 1H, *m*-C*H*, arom), 6.96–6.94 (m, 2H, C*H*, arom), 6.73–6.70 (m, 1H, C*H*, arom), 4.61 (d, ^4J=2.5 Hz, 2H, O-CH_2), 2.43 (t, ^4J=2.5 Hz, 1H, C≡C*H*), 1.23 (s, 9H, *t*-Bu); ^{13}C{^{1}H} NMR ($CDCl_3$): δ=156.4, 152.1, 127.9, 117.7, 112.0, 109.9, 77.8, 74.3, 54.7, 33.7, 30.2; MS: m/z=189 $[M+H]^+$.

***sec*-Hexyl 3-*tert*-butylphenyl ether:** ^{1}H NMR ($CDCl_3$): δ=7.12 (t, ^3J=7.5 Hz, 1H, *m*-C*H*, arom), 6.89–6.84 (m, 2H, C*H*, arom), 6.63–6.61 (m, 1H, C*H*, arom), 4.27 (tq, ^3J=6 Hz, 1H, O-C*H*), 1.71–1.65 (m, 1H, O-CHCH_2), 1.52–1.46 (m, 1H, O-CHCH_2), 1.41–1.29 (m, 4H, CH_2), 1.23 (s, 9H, *t*-Bu), 1.22 (d, ^3J=7 Hz, 3H, O-CHCH_3), 0.84 (t, ^3J=7.5 Hz, 3H, CH_2CH_3); ^{13}C{^{1}H} NMR ($CDCl_3$): δ=157.0, 151.9, 127.8, 116.5, 113.0, 110.9, 72.6, 35.3, 33.7, 30.3, 26.8, 21.7, 18.8, 13.0; MS: m/z=235 $[M+H]^+$.

4-Bromobenzyl chloroacetate: ^{1}H NMR ($CDCl_3$): δ=7.42 (d, ^3J=8.5 Hz, 2H, CH, arom), 7.16 (d, ^3J=8.5 Hz, 2H, CH, arom), 5.08 (s, 2H, O-CH_2), 4.01 (s, 2H, $COCH_2$); ^{13}C{^{1}H}

NMR ($CDCl_3$): δ=166.0, 132.9, 130.8, 129.1, 121.8, 66.0, 39.8; MS: m/z=212, 214 $[M\text{-}CH_3Cl]^+$.

***n*-Propyl *p*-*sec*-butoxybenzoate:** ^1H NMR ($CDCl_3$): δ= 7.98 (d, ^3J=9.3 Hz, 2H, C*H*, arom), 6.89 (d, ^3J=9.0 Hz, 2H, C*H*, arom), 4.38 (tq, ^3J=6 Hz, 1H, O-C*H*), 4.24 (t, ^3J= 6.3 Hz, 2H, $COOCH_2$), 1.83–1.30 (m, 4H, CH_2), 1.31 (d, ^3J=6 Hz, 3H, $CHCH_3$), 1.04–0.94 (m, 6H, CH_2CH_3); $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ=166.5, 162.1, 131.6, 122.5, 115.0, 75.1, 66.2, 29.1, 22.2, 19.1, 10.6, 9.7; MS: m/z=237 $[M+H]^+$.

***N*-*sec*-Hexylphthalimide** (CAS 221155-51-7): ^1H NMR ($CDCl_3$): δ=7.74–7.72 (m, 2H, C*H*, arom), 7.63–7.61 (m, 2H, C*H*, arom), 4.26 (tq, ^3J=7 Hz, 1H, N-C*H*), 2.02–1.94 (m, 1H, $CHCH_2$), 1.69–1.62 (m, 1H, $CHCH_2$), 1.38 (d, ^3J= 7 Hz, 3H, $CHCH_3$), 1.29–1.07 (m, 4H, CH_2), 0.77 (t, ^3J= 7.5 Hz, 3H, CH_2CH_3); $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ=167.5, 132.7, 131.0, 122.0, 46.5, 32.4, 27.9, 21.3, 17.7, 12.9; MS: m/z=233 $[M+H]^+$.

***N*-2-Ethylhexylphthalimide:** ^1H NMR ($CDCl_3$): δ=7.85–7.82 (m, 2H, C*H*, arom), 7.72–7.70 (m, 2H, C*H*, arom), 3.58 (d, ^3J=7.5 Hz, 2H, N-CH_2), 1.84 (tt, ^3J=6.5 Hz, 1H, N-CH_2CH), 1.41–1.25 (m, 8H, CH_2), 0.92 (t, ^3J=7.5 Hz, 3H, ethyl-CH_3), 0.88 (t, ^3J=7.5 Hz, 3H, hexyl-CH_3); $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ=167.7, 132.8, 131.1, 122.1, 40.9, 37.3, 29.5, 27.5, 22.9, 22.0, 13.0, 9.4; MS: m/z=260 $[M+H]^+$.

Recovery of FcTPPO (3)

The combined aqueous phases of a Mitsunobu reaction (as described above), containing Diphenyl-FcTPPO$^+$ (**3**$^+$) were treated with saturated $Na_2S_2O_3$ solution (50 mL). After addition of THF (30 mL) the mixture was stirred for 15 min at ambient temperature, then extracted with Et_2O (3×30 mL). The combined organic phases were washed with brine, dried with $MgSO_4$ and filtered. Removal of the volatiles under vacuum afforded 580 mg of crude product. Further purification through a short plug of silica gel (6 cm, elution of impurities with cyclohexane/ethyl acetate, 10:1, then elution of the ferrocene with cyclohexane/ethyl acetate, 1:9) afforded pure FcTPPO as a red-orange solid; yield: 500 mg (1.08 mmol, 83%); R_f 0.38. (1:9 cyclohexane/EtOAc). ^1H NMR (benzene-d_6): δ=7.86–7.82 (m, 4H, arom), 7.76–7.72 (m, 2H, arom), 7.30–7.27 (m, 2H, arom), 7.08–7.02 (m, 6H, arom), 4.41 (t, J=2.0 Hz, 2H, Fc), 4.11 (t, J=2.0, 2H, Fc), 3,82 (s, 5H, Fc); $^{13}C\{^1H\}$ NMR (DMSO-d_6): δ=144.1, 133.8, 133.0, 132.3, 132.0, 131.84 (d, $J_{P,C}$=9.3 Hz), 129.1 (d, $J_{C,B}$=11.1 Hz), 126.3 (d, $J_{P,C}$=12.3 Hz), 83.3, 70.0, 69.9, 67.2; ^{31}P NMR (acetone-d_6): δ=25.70; ^{31}P NMR (DMSO-d_6): δ=23.99; anal. calcd. for $C_{28}H_{23}FeOP$ (462.3): C 72.8, H 5.02; found: C 73.9, H 5.55.

Reduction of FcTPPO (3)

FcTPPO (**3**) (450 mg, 0.97 mmol) was dissolved in absolute toluene (7 mL) and placed in a pressure tube under an argon atmosphere. TEA (1.5 mL) and $HSiCl_3$ (1.0 mL) were added and the reaction mixture was stirred at 120°C for 12 h. The mixture was cooled to room temperature, 20 mL H_2O were added before extraction with Et_2O (3×20 mL). The combined organic phases were washed subsequently with water (15 mL) and brine (15 mL), dried with $MgSO_4$ and filtered. Removal of volatiles under vacuum afforded **2** as a red viscous oil; yield: 431 mg (100%). ^1H, ^{13}C and ^{31}P NMR spectra were found to be identical with those described above for FcTPP.

Acknowledgements

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4.11. cataCXium® F

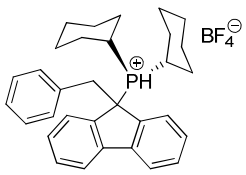
Die in dieser Arbeit beschriebenen Liganden der Fluorenyldialkylphosphin-Klasse wurden zusammen mit der Firma Evonik-Degussa GmbH patentiert:

Herbert Plenio, Christoph Fleckenstein, Renat Kadyrov, Juan Almena, Axel Monsees, Thomas Riermeier (Evonik Degussa GmbH), *„New Cyclopentadienyl, Indenyl or Fluorenyl Substituted Phosphine Compounds and their Use in Catalytic Reactions"*, WO2008025673, **2008**.

Einige Vertreter dieser Liganden sind mittlerweile unter dem Handelsnamen

cataCXium® F

z.B. über *STREM* oder *Aldrich* kommerziell erhältlich:



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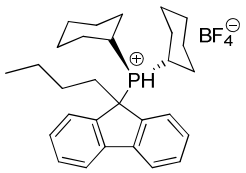

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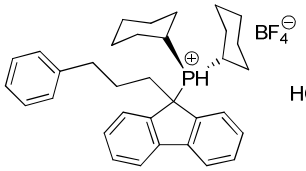

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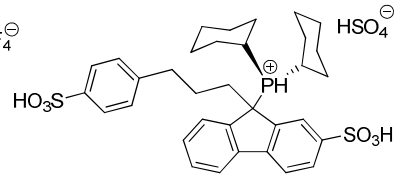


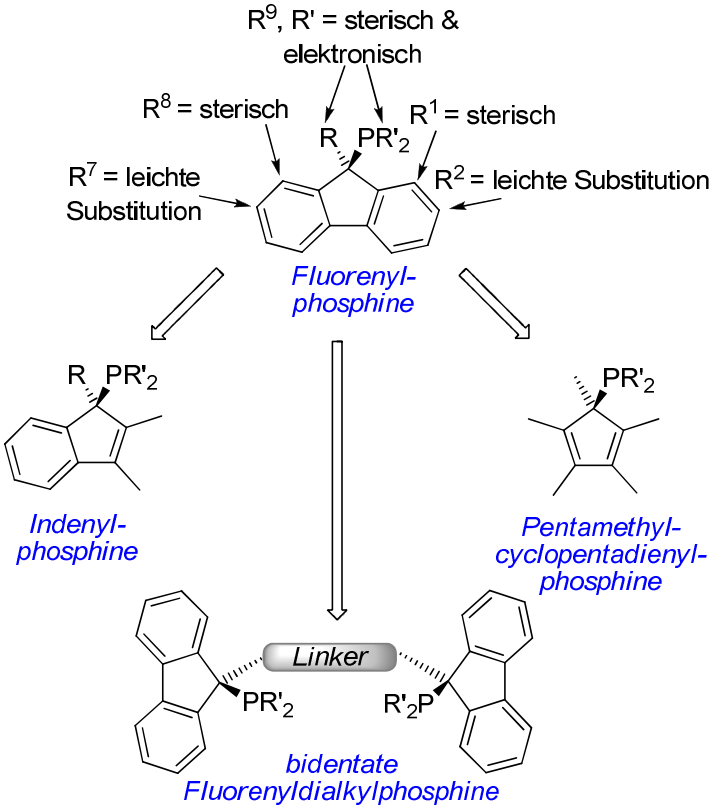
cataCXium® FSulf
CAS: 1020540-69-5

5. Zusammenfassung

Die vorliegende Arbeit beschreibt die erfolgreiche, rationale Entwicklung der Ligandenklasse der Fluorenyldialkylphosphine, die inzwischen durch die *Evonik-Degussa GmbH* unter dem Handelsnamen *cataCXium® F* in den Markt eingeführt werden konnte. Durch Einbau der Fluorenylstruktur sind nun Phosphinliganden verfügbar, deren Pd-Komplexe über außergewöhnlich hohe katalytische Aktivität verfügen, aber gleichzeitig hochvariabel und preiswert synthetisierbar sind. Ein doppelt sulfonierter Vertreter der neuen Ligandenklasse, *cataCXium® FSulf*, bildet hervorragend wasserlösliche Palladiumkomplexe, die neue Maßstäbe in der Entwicklung nachhaltiger Kreuzkupplungsreaktionen setzen. Im Folgenden werden die Eigenschaften der Fluorenyldialkylphosphine zusammenfassend erläutert:

1. Variabilität

Die entwickelten Fluorenyldialkylphosphine verfügen über eine ausgesprochen große Variabilität. Hierdurch lassen sich die für die katalytische Aktivität entscheidenden sterischen und elektronischen Eigenschaften flexibel einstellen. Das nebenstehende Schema verdeutlicht die vielen Möglichkeiten, Fluorenylphosphine sterisch und elektronisch zu variieren. Die Positionen 2 und 7 am Fluorengerüst sind mit S_E-Reaktionen zugänglich. Diese Positionen eignen sich in hervorragender Art und Weise zur Funktionalisierung, beispielsweise zur polaren Phasenmarkierung der Liganden durch Einführen einer Sulfonsäuregruppe. Darüber hinaus stehen mit den verwandten Phosphinen auf Indenyl- bzw. Pentamethylcyclopentadienyl-Basis weitere Liganden mit einem strukturell ähnlichen Grundkörper zur Verfügung. Dies eröffnet weitere Möglichkeiten der Variation der Fluorenylphosphin-Ligandenfamilie. Die Alkylgruppe in Position 9 des Fluorenylrests kann auch



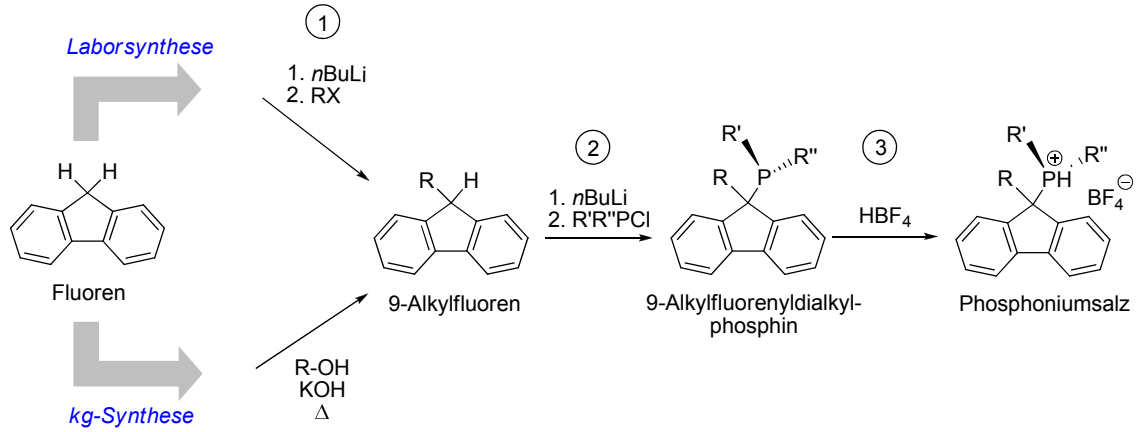
als Linker zwischen zwei Phosphinen des neuen Typs fungieren. Hierdurch sind hochaktive bidentate Diphosphine zugänglich, deren Aktivität und Selektivität über die Länge und Art des Linkers steuerbar sind. Unter dem Gesichtspunkt der hier aufgezeigten vielschichtigen Variabilität des Fluorenylphosphinsystems wurden 37 verschiedene Phosphine synthetisiert. Ihre Strukturen sind dem angehängten Faltblatt zu entnehmen.

2. Synthese der Fluorenyldialkylphosphine

Die beschriebenen Fluorenyldialkylphosphine wurden im Labormaßstab, wie im unten aufgeführten Schema gezeigt, synthetisiert. Die Synthese der Indenyl- und Pentamethylcyclopentadienylphosphine erfolgte analog:

1.) Synthese des entsprechenden 9-substituierten Alkylfluorens durch Deprotonierung von Fluoren mit *n*BuLi und anschließender S_N-Reaktion des Fluorenylanions mit einem Alkylhalogenid
2.) Deprotonierung des 9-Alkylfluorens mit einer starken Base (*n*BuLi oder LDA), Reaktion des Anions mit dem entsprechenden Dialkylphosphinchlorid
3.) Protonierung des Phosphins mit HBF_4 und Isolation als luftstabiles Phosphoniumsalz

Auf diese Weise gelang die Darstellung zahlreicher, in sterischen und elektronischen Eigenschaften verschiedener Phosphine der Fluorenyldialkylphosphinklasse in hoher Reinheit (>99 %) und in Ausbeuten bis zu 90 %.



Die Laborsyntheseroute ließ sich nicht problemlos auf den kg-Maßstab übertragen. Der Laborsyntheseschritt ① erfolgt mit ungenügender Selektivität unter Bildung nicht-, mono- und dialkylierter Fluorene. Großtechnisch lassen sich Monoalkylfluorene selektiv und in hoher Ausbeute basenkatalysiert aus Fluoren und dem entsprechenden Alkylalkohol darstellen. Ein entsprechend entwickeltes Verfahren erlaubt die preiswerte ausbeute-

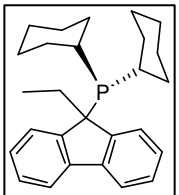
optimierte Synthese hochaktiver Fluorenylphosphinliganden im kg-Maßstab, typischerweise in Ausbeuten über 90 %.

3. Katalytische Aktivität

In situ gebildete Palladiumkomplexe der Fluorenyldialkylphosphine sowie die entsprechenden bidentaten Analoga stellten sich als hochaktive Katalysatoren für Sonogashira-, Suzuki- und Buchwald-Hartwig-Aminierungsreaktionen mit Arylbromiden und Arylchloriden heraus. In wichtigen Anwendungsbereichen erweisen sich Fluorenylphosphin-Palladiumkomplexe als die derzeit aktivsten literaturbekannten katalytischen Systeme:

- *Sonogashira-Kreuzkupplungen mit Brom- und Chloraromaten*

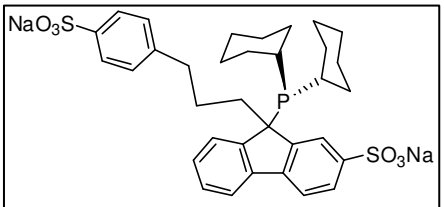
Pd-Komplexe des Liganden EtFluPCy$_2$ ermöglichen beispielsweise die Kupplung deaktivierter Substrate wie *p*-Brombenzol mit Phenylacetylen mit unerreicht hohen Katalysatoraktivitäten (TON = 5600 bei 50 °C Reaktionstemperatur; TON >25000 bei 90 °C). Quantitative Kupplungen von Bromaromaten lassen sich problemlos mit einer Katalysatorbeladung von 0.02 mol% bewerkstelligen. Bei der Kupplung von Chloraromaten zeigten sich Pd-Komplexe mit EtFluPCy$_2$ dem bisher aktivsten System mit Diadamantylbenzylphosphin als Ligand überlegen. Für Sonogashira-Reaktionen demonstriert Pd/EtFluPCy$_2$ somit unerreichte Aktivitäten.



EtFluPCy$_2$

- *Suzuki-Kupplungen heterocyclischer Substrate*

Heterocyclen sind Substrate von besonderem Interesse für die pharmazeutische Chemie, Agro- und Feinchemie und sind als schwierige Kupplungspartner in übergangsmetallkatalysierten Kreuzkupplungen bekannt. Zum einen stellen Heterocyclen oft gute Donorliganden dar und bewirken eine Katalysatordeaktivierung durch kompetitive Inhibierung. Zum anderen erfordern heterocyclische Substrate häufig milde Reaktionsbedingungen, lassen jedoch keine längeren Reaktionszeiten zu. Palladiumkomplexe mit dem doppelt sulfonierten Fluorenylphosphinliganden *cataCXium® FSulf* erlauben effiziente Suzuki-Kupplungen verschiedenster heterocyclischer Substrate in Wasser oder *n*-Butanol/Wasser-Mischungen als Reaktionsmedium. Katalysatorbeladungen von 0.005-0.5 mol% ermöglichen quantitativen Umsatz von Chloraromaten. Somit ist Pd/*cataCXium® FSulf* bis



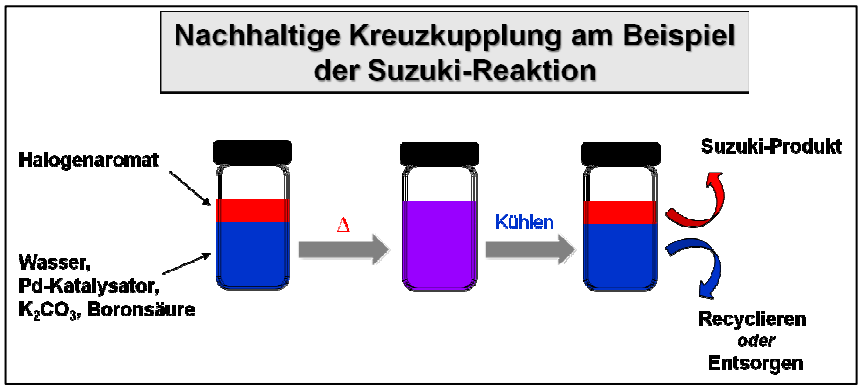
cataCXium® FSulf

zu 100 mal aktiver als Palladiumkomplexe mit Buchwald-Biphenylphosphinen wie XPhos oder SPhos, welche bis zu jenem Zeitpunkt die aktivsten Systeme zur Suzuki-Kupplung von *N*- und *S*-Heterocyclen darstellten. Die folgende Aufzählung demonstriert einen Ausschnitt aus der großen Bandbreite der mit Pd/*cataCXium® FSulf* kuppelbaren Heterocyclen:

- deaktivierte nichtheterocyclische Chloraromaten
- Chlorpyridine
- Chlorchinoline
- Aromaten mit freien Aminofunktionalitäten
- Chlorpurine
- Chlorthiophene
- Chlorbenzothiazole
- Phenylboronsäuren
- Naphthylboronsäuren
- Pyridinboronsäuren
- Indolboronsäuren
- Thiophenboronsäuren
- Furanboronsäuren

4. Entwicklung nachhaltiger Kreuzkupplungsverfahren

Palladium/*cataCXium® FSulf*-Komplexe sind hochwasserlöslich und hervorragende Katalysatoren für Kreuzkupplungsreaktionen in wässrigen Reaktionsmedien. Dies ermöglicht die Entwicklung nachhaltiger Kreuzkupplungsprotokolle, beispielsweise in reinem Wasser als Lösemittel, wie im Schema (*vide infra*) abgebildet. Der wasserlösliche Katalysator, anorganische Reagenzien (Basen) und ggf. benötigte Boronsäure sind in der wässrigen Phase gelöst, der im Allgemeinen lipophile Halogenaromat bildet die organische Phase. Nach erfolgter Reaktion trennt sich bei Raumtemperatur das Produkt als organische Phase ab und ist ohne Zusatz weiterer organischer Lösemittel leicht physikalisch separierbar. Bei quantitativem Umsatz des Halogenaromaten lässt sich das Rohprodukt in Ausbeuten >90 % und Reinheiten >98 % ohne weiteren Reinigungsschritt isolieren. Die den Katalysator beinhaltende wässrige Phase kann im Rahmen eines kontinuierlichen Prozesses einer neuen Katalysereaktion zugeführt werden. Das Verfahren eignet sich bevorzugt für Kreuzkupplungen der Größenordnung >10 mmol. Durch den Zusatz von Isopropanol als biologisch leicht abbaubares Cosolvens lässt sich das entwickelte wässrige Reaktionsprotokoll auch bei kupferfreien Sonogashira-Kreuzkupplungen anwenden.



Für die Nachhaltigkeit des Verfahrens stehen folgende Eckpunkte:

- Wasser und Alkohole als preiswerte, ungiftige und biologisch abbaubare Reaktionsmedien
- K_2CO_3 als preiswerte und unbedenkliche Base
- effiziente Katalyse im technischen Maßstab
- leichte Produktisolation; kein Zusatz weiterer organischer Lösemittel
- hohe Produktausbeute und -reinheit

6. Ausblick

Hochwasserlösliche Palladiumkomplexe mit dem doppelt sulfonierten Fluorenyldialkylphosphinliganden *cataCXium® FSulf* sind aus zwei Gründen interessante Katalysatoren für Kreuzkupplungsreaktionen:

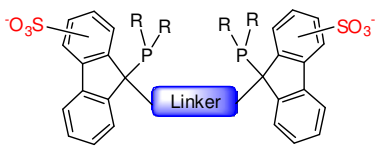
- Sie offenbaren in wässrigen Reaktionsmedien beispiellose katalytische Aktivitäten, insbesondere hinsichtlich der Kupplung industriell wichtiger heterocyclischer Substrate.
- Sie ermöglichen die nachhaltige Reaktionsführung von Kreuzkupplungen in wässrigen bzw. biologisch abbaubaren wässrig/alkoholischen Reaktionsmedien. Die Produktisolation ist ohne Zusatz organischer Lösemittel möglich.

➡ Somit liegt es nahe, weitere Arbeiten im Fokus der Stärken dieses katalytischen Systems voranzutreiben. Beispielsweise ist zu testen, ob Pd/*cataCXium® FSulf* auch *α*-Arylierungsreaktionen oder Buchwald-Hartwig-Aminierungen/Veretherungen in wässrigen oder wässrig/alkoholischen Reaktionsmedien ermöglicht.

Ein weiterer Ansatzpunkt für zukünftige Untersuchungen ergibt sich ebenfalls zwangsläufig aus der vorliegenden Dissertation:

- Es ist aus der Literatur bekannt, dass bidentate Diphosphine stabile Pd^0-Komplexe ausbilden. Diese Komplexe sind oft aktivere Katalysatoren zur Kreuzkupplung heterocyclischer Substrate als Pd/Monophosphinkomplexe.
- Durch die vorliegende Dissertation ist weiterhin bekannt, dass sich die Verwendung wässriger Reaktionsmedien signifikant positiv auf die katalytische Aktivität von Pd-Katalysatoren bei der Kupplung heterocyclischer Substrate auswirkt. Durch polare Phasenmarkierung z.B. mittels Sulfonatogruppen kann eine Optimierung des Katalysators durch Adaption an das Reaktionsmedium erfolgen.

➡ Ein rationales Katalysatordesign, d.h. die Entwicklung neuer, besserer Katalysatoren aufgrund bekannter Erkenntnisse, legt somit nahe, die bereits vorhandenen bidentaten Difluorenyldiphosphine zu sulfonieren. Sinnvoll ist die Sulfonierung des methylenverbrückten Difluorenyldiphosphinliganden, da sich dieser als der aktivste Ligand in Suzuki- und Aminierungsreaktionen zeigte. In vergleichenden anspruchsvollen Testreaktionen, beispielsweise Suzuki-Kupplungen ungeschützter Chlorpurine, ist die erwartete Aktivitätssteigerung der neuen resultierenden Katalysatoren anschließend zu überprüfen.



Difluorenyldiphosphin
(zweizähnig, wasserlöslich)

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Eidesstattliche Erklärung

Ich erkläre hiermit an Eides statt, dass ich meine Dissertation selbständig und nur mit den angegebenen Hilfsmitteln angefertigt habe.

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Erklärung

Ich erkläre hiermit, noch keinen Promotionsversuch unternommen zu haben.

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